A mortality study of workers exposed to insoluble forms of beryllium
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This study investigated lung cancer and other diseases related to insoluble beryllium compounds. A cohort of 4950 workers from four US insoluble beryllium manufacturing facilities were followed through 2009. Expected deaths were calculated using local and national rates. On the basis of local rates, all-cause mortality was significantly reduced. Mortality from lung cancer (standardized mortality ratio 96.0; 95% confidence interval 80.0, 114.3) and from nonmalignant respiratory diseases was also reduced. There were no significant trends for either cause of death according to duration of employment or time since first employment. Uterine cancer among women was the only cause of death with a significantly increased standardized mortality ratio. Five of the seven women worked in office jobs. This study confirmed the lack of an increase in mortality from lung cancer and nonmalignant respiratory diseases related to insoluble beryllium compounds. \textit{European Journal of Cancer Prevention} 23:587–593 \textcopyright 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: beryllium, lung cancer, mortality, retrospective cohort

Introduction
An increased mortality from lung cancer has been reported in workers from two beryllium facilities in the USA that were in operation in the 1940s (Mancuso, 1980; Wagoner \textit{et al.}, 1980; Ward \textit{et al.}, 1992). The increased risk was restricted to workers in these two facilities who were first employed before 1960, as workers hired after that date and workers employed in five other US facilities did not experience an excess lung cancer risk (Ward \textit{et al.}, 1992). Several analyses have been carried out in different subsets of these workers (Sanderson \textit{et al.}, 2001; Levy \textit{et al.}, 2002, 2007, 2009; Schubauer-Berigan \textit{et al.}, 2011a, 2011b), as well as in a partially overlapping series of patients included in a registry of beryllium disease (Infante \textit{et al.}, 1980; Steenland and Ward, 1991). In a recent comprehensive review, Boffetta \textit{et al.} (2012) showed that the association between beryllium exposure and lung cancer risk depends upon the inclusion of highly exposed workers who were employed during the early technological phase in the two original US plants (Lorain and Reading) and those who were exposed to high levels of beryllium, including soluble beryllium compounds formed as intermediates within the extraction process. It is unclear whether these results reflect a small risk for lung cancer following very high exposure to soluble beryllium, result from confounding by lifestyle or occupational factors, and are relevant to workers employed in the modern commercial beryllium industry in which there is exposure only to insoluble beryllium. A limitation of the body of evidence on beryllium exposure and lung cancer is that results and conclusions are largely based on subsequent analyses of the same data set.

We undertook this study to complement the information provided by the seven-plant study on the risk for lung cancer and other diseases among beryllium workers by analyzing data on workers exposed to insoluble beryllium and mostly not included in previous studies. The goal was to provide results that are directly relevant to the exposure circumstances of currently employed workers.

Methods
This historical cohort mortality study includes employees who worked at four beryllium manufacturing facilities that only processed the insoluble forms of metallic beryllium, beryllium-containing alloys (primarily copper beryllium) and beryllium oxide. These facilities are located in three states, Pennsylvania, Arizona, and Ohio (Table 1). The Cleveland facility consisted of two individual plants (Perkins and St Clair) located close to each other in Cleveland, Ohio. Because of the proximity, both plants used the same employee forms; hence, it is not possible to determine at which specific plant the employees worked. Beryllium operations at the Perkins plant included producing metal powder, vacuum hot pressing, powder consolidation, and machining. Beryllium operations at the St Clair plant consisted of the machine shop, which was transferred from the Perkins plant in the early 1960s, and research and development. The Shoemakerville plant, located in Reading, Pennsylvania, processes beryllium-containing alloys to produce strip, rod, and wire products. The Reading plant, which was also in Reading, Pennsylvania, produced beryllium copper

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ally. Only employees hired at the Reading plant after 1965 were included in the cohort, as beryllium ore refining and beryllium oxide production operations were performed at the facility before 1965, meaning employees hired in this time period would have been exposed to both soluble and insoluble beryllium. The Tucson plant, located in Tucson, Arizona, produces beryllium oxide ceramic products.

Employees had to have worked for at least one day before 31 December 2009 at one of the plants to be eligible for inclusion in the cohort. The earliest date of hire ranged from 1947 to 1980 among the plants. Numerous sources of data were used to enumerate the cohort, including employment records, electronic files, and payroll information. Wherever possible, original employment records related to the establishment of the cohort were reviewed to ensure that the abstraction and computerization of the data were error free. Consistency checks were also performed on the database before updating the cohort. Any errors and omissions that were identified were corrected before analysis.

The following rules were applied to the database. Hire date was considered date of hire at any one of the plants, and person-years began to accumulate one day after hire. Termination date was the last known date of employment or the date of death. When termination dates were missing, the termination date was considered the earlier of either the last date the plant was operational, the end of the study, or the date of death. Missing hire dates (N = 2) were assumed to be the date of the first known job. For employees with no detailed work history information (N = 35), hire date was set to the first date the plant was operational. Thirty employees missing multiple data fields essential for the analysis (which could not be assumed as outlined above) were excluded from the analyses. Employees who worked in more than one of the facilities were included once in the analyses for all plants combined for their entire duration of employment, whereas they were included in individual plant analyses for the length of employment at that particular plant.

Vital status was ascertained through 31 December 2009 using data from the National Center for Health Statistics’ National Death Index (NDI). The NDI is considered a complete and accurate source of mortality information on US citizens whose deaths have occurred after 1 January 1979. Cause of death information coding for individuals identified in the NDI database was obtained through NDI Plus. Employees not identified in the NDI databases who were still working after 1979 were presumed to still be alive as of the end of study date.

Vital status before 1979 was ascertained through Social Security Administration (SSA). For suspected and known deaths that occurred before 1979, information on the state of death was obtained from the SSA and death certificates were requested from the appropriate states. A copy of the verified death certificates was sent to a professional nosologist for coding to the International Classification of Diseases (ICD) revision in effect at the time of death. Employees who were not located through NDI or the SSA, or who had no other vital status information available in the company records (N = 221) were considered lost to follow-up as of their date of termination of employment.

Mortality analyses were based on cause-specific standardized mortality ratios (SMRs), which were calculated by dividing the number of observed deaths by the number of deaths that were expected to occur. Mortality in the USA was used as a reference in the analyses examining all plants combined. For plant-specific analyses, appropriate regional mortality rates were selected as references after examining demographic and socioeconomic characteristics of comparable areas surrounding the plants (i.e. the county where the plant was located and similar neighboring counties). The mortality experience of the cohort was examined for all plants combined, by sex and by individual manufacturing facility, and SMRs and their 95% confidence intervals (CIs) were calculated after adjustment for age, sex, race, and calendar period using the University of Pittsburgh’s OCMAP program. Only underlying causes of death were included in the analyses. Overall, 63 causes of death were examined. Because the results of some of the previous studies on beryllium workers employed before 1960 have suggested an association between beryllium exposure and lung cancer, this constituted the primary outcome of interest. Both observed deaths and person-years of workers with

### Table 1 Facilities included in the study

| Facility            | First hire date | Last hire date | N   | Reference population                                      |
|---------------------|-----------------|----------------|-----|-----------------------------------------------------------|
| Reading post 1965b  | 1/1/1966        | 12/2/1998      | 824 | Berks, Lancaster, and Lebanon (PA) counties               |
| Shoemakersville     | 9/1/1953        | 3/19/2007      | 690 | Berks, Lancaster, and Lebanon (PA) counties               |
| Tucson              | 1/2/1980        | 4/29/2008      | 1172| Pima and Maricopa (AZ) counties                           |
| Clevelandb,c        | 1/1/1947        | 2/12/2008      | 2277| Cuyahoga and Summit (OH) counties                         |
| All plants combined | 1/1/1947        | 4/29/2008      | 4950| Berks, Lancaster, and Lebanon (PA) counties, Pima and Maricopa (AZ) counties, and Cuyahoga and Summit (OH) counties|

*For this plant, employees who worked in more than one plant were included in the totals for each individual plant, but only once overall with combined dates.

*Some of the workers employed at these facilities were included in a previous cohort (Ward et al., 1992).

*The Cleveland facility includes two plants (Perkins and St Clair).
unknown race \((N = 2292)\) were proportionally allocated on the basis of the proportion of employees in the cohort with known white race (Marsh et al., 1998).

Membership in the cohort was used as a surrogate measure of potential occupational exposures. As detailed work history information was not available for \(\approx 30\%\) of the cohort, we were unable to use job type as a surrogate for level of exposure. However, analyses by length of employment served as an indirect measure of exposure in the absence of exposure-monitoring data. Continuous employment was assumed, although sensitivity analyses were also carried out to account for workers with breaks in their employment history and to examine the effect of these gaps in exposure on the results. Analyses were also carried out to examine mortality from interval since hire as a surrogate for latency to permit examination of disease (mortality) to elapsed time since ‘exposure’ first occurred, as certain chronic diseases require sufficient time to develop.

**Results**

There were 4950 employees in the four beryllium facilities with insoluble operations (Table 1). The largest facility, Cleveland, contributed 45% of the cohort and the smallest facility, Shoemakersville, contributed 14% of the cohort (Table 1). Overall, 3912 (79.8%) men and 1038 (21.2%) women were included in the cohort. Workers were predominantly white (95.3%). Of the total person-years of observation (143 670), 76.0% (109 201) were contributed by white men.

A total of 1480 deaths from all causes occurred over the study period (Table 2). The SMRs using US rates as a comparison were slightly, but not appreciably, lower than the SMRs using combined county rates. Therefore, only
results using the combined county rates are presented. The results obtained using US data as the comparison are reported in Supplementary Table B.

The SMR for all causes was significantly reduced (SMR = 94.7; 95% CI 89.9, 99.7), largely because of the reduced SMRs for two large categories of death, heart disease (n = 481; SMR = 95.0; 95% CI 86.7, 103.9) and external causes of death (n = 99; SMR = 81.4; 95% CI 66.1, 99.1). Observed and expected numbers of deaths from all cancers were essentially the same (SMR = 99.8). The observed number of deaths from lung cancer was less than expected (n = 7; SMR = 302.3; 95% CI 121.5, 622.9). Five of the seven women who died from uterine cancer worked in office jobs: three worked for less than 1 year and three worked for between 1 and 3 years.

For the total cohort there was no noteworthy trend by number of years of employment for any specific cause of death (Table 3). Among workers with 20 or more years of employment, the SMR for lung cancer was 112.7 (95% CI 68.6, 178.1), on the basis of 18 deaths, and that for nonmalignant respiratory diseases was 136.8 (n = 22; 95% CI 85.7, 207.1). A test for trend was not statistically significant for either cause of death (P-values = 0.40 and 0.07, respectively). There was no significantly increased SMR for any specific cause of death among the longest term employees. These results were similar for men (Supplementary Table D).

For the longest category of time from hire (hereafter referred to as latency), the SMRs for lung cancer and other nonmalignant respiratory diseases were not significantly increased, although there was an increase in SMR with increasing latency (Table 4). A test for trend was not statistically significant for either cause of death (P-values = 0.24 and 0.33, respectively). The results for men were similar (Supplementary Table E).

An analysis of the stratified data on employment start date before or after 1960 did not alter the conclusions (data not shown). The SMRs were generally slightly lower than expected.

Uterine cancer among women was the only cause of death with a significantly increased SMR (n = 7; SMR = 302.3; 95% CI 121.5, 622.9). Five of the seven women who died from uterine cancer worked in office jobs: three worked for less than 1 year and three worked for between 1 and 3 years.

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lower in the post-1960 period. In the post-1960 period, the SMR for all causes of death was significantly reduced (89.3) largely because of the reduced SMR for heart disease (90.0) and external causes of death (91.6). For lung cancer, the SMRs were 102.9 (95% CI 80.2, 130.0, 70 deaths) for the pre-1960 start date period and 89.8 (95% CI 67.8, 116.6, 56 deaths) for the post-1960 start date period.

When the data were analyzed by start date (pre-1960 and post-1960) and latency, the results showed that the increase in SMR with increasing latency was confined to the pre-1960 start dates for lung cancer, although the trend and the SMR for the longest latency period were not statistically significant (Tables 5 and 6). There was no increasing trend for nonmalignant respiratory diseases during the three latency periods for either the pre-1960 or post-1960 start dates. The results for men only were essentially the same (Supplementary Tables F and G).

**Discussion**

The results of this study do not support the hypothesis that exposure to insoluble beryllium causes an increased risk for lung cancer of the order of 20% or higher. They are consistent with a recent review that concluded that the increased mortality from lung cancer reported among workers employed in the early technological phase in two beryllium plants is not confirmed in studies on workers employed later on (Boffetta et al., 2012). Workers in these two plants were involved in the extraction of beryllium, which entails the formation of soluble beryllium compounds as intermediates. Soluble forms of beryllium are not used commercially; only insoluble metallic products and beryllium oxide are in commerce. Whether the excess lung cancer mortality among workers employed in the early technological period of the industry can be attributed to exposure to beryllium (and specifically soluble beryllium) or to other factors remains undetermined. In contrast, the lack of increased lung cancer risk among workers employed in the ‘modern’ beryllium industry, with exposure restricted to insoluble beryllium, is supported by the results of this study.

As beryllium workers are currently exposed to beryllium in the form of relatively insoluble particles such as beryllium compounds (e.g. beryllium oxide) or metal, our study was restricted to workers exposed to this group of agents. Our results are consistent with the data on carcinogenicity of insoluble beryllium in experimental animals, which point toward a mechanism of lung overload in rats that is not relevant to humans (Strupp, 2011).
The only cause of death for which there was a statistically significantly increased mortality was cancer of the uterus, on the basis of seven observed deaths. Cancers originating from the two parts of the uterus (cervix, $n = 2$, and corpus, $n = 5$) have very different epidemiological, molecular, and clinical characteristics and no overlap in known risk factors (Cook et al., 2006; Schiffman and Hildesheim, 2006). Further, six of the deceased workers were employed for less than 3 years. The most likely explanation for this finding, therefore, remains chance because of multiple comparisons.

The analysis of mortality from non-neoplastic causes did not reveal any increased risk in this cohort. A small, nonsignificant excess of mortality from non-neoplastic respiratory diseases was observed among workers with 20 years or more of employment or 30 years of latency, which was due to non-neoplastic diseases other than chronic bronchitis and emphysema, a category that includes deaths from chronic beryllium disease (CBD). In particular, CBD (ICD-8 code 516.0, ICD-9 code 503, or ICD-10 code J632) was the underlying cause of death of 12 cohort members. They were part of a group of 52 cohort members, whose cause of death was classified as ‘other nonmalignant disease of the respiratory system’. We were able to obtain the death certificate for 21 of these 52 deceased cohort members, including four with CBD as the underlying cause. A reference to beryllium or beryllium disease was present on an additional two certificates, which had a different underlying cause (2/17, or 12%). If the 21 certificates were a representative sample, and CBD-related deaths were not included in other ICD categories, between 12 and 17 [12 + 12% of (52 – 12)] deaths in this cohort were due to CBD. Although no definitive conclusions can be drawn from these results and a longer follow-up of this cohort is needed for more conclusive evidence, the fact that we identified deaths from CBD supports the notion that these workers were indeed exposed to beryllium, and the lack of increased risk for lung cancer is not due to lack of opportunity of exposure. Further, these results argue against the hypothesis of common mechanistic pathways (e.g. beryllium-induced inflammation) for CBD and lung cancer (Sawyer et al., 2005).

The main strengths of this study lie in its prospective design, the completeness of the enumeration of the cohort, and the high success rate in follow-up. The relatively large size of the study is an additional strength. Although a small risk for lung cancer is compatible with our results, we can confidently exclude an excess greater than 20%. Limitations include the lack of information on job titles and quantitative exposure to beryllium; the lack of information on jobs outside the beryllium industry (72% of cohort members were employed for less than 5 years); and the lack of information on nonoccupational cancer risk factors, mainly tobacco smoking, although the lack of excess mortality from other tobacco-related causes argues against a strong confounding effect. The effect of factors other than employment in the beryllium industry was partially offset by the use of regional mortality rates as a reference. The lack of excess in causes associated with other occupational exposures and lifestyle factors, such as tobacco smoking, alcohol drinking, and obesity, argues against an important role of residual confounding.

Conclusion
This study on beryllium workers employed at four facilities and exposed to insoluble beryllium does not provide evidence of an increased risk of lung cancer or any other neoplastic or non-neoplastic disease. The results support the conclusions of previous reviews that the increased mortality from lung cancer identified among workers employed in the early technological phase of the industry with high exposure to soluble beryllium is not relevant to the risk among workers employed in this industry under ‘modern’ circumstances entailing exposure to insoluble beryllium.

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Conflicts of interest
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