An Updated Mortality Study of Beryllium Workers, 1925–2020

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Objective: Update and expand a cohort of beryllium workers, to examine risks associated with beryllium solubility and mortality from lung cancer, all cancers, all causes, as well as other neoplasms (kidney, bladder, central nervous system) and other nonmalignant respiratory disease. **Methods:** The study conducted a retrospective cohort study of 17,149 workers employed in 15 US facilities (1925–2020). Data were analyzed using standardized mortality ratios referencing the US population and Cox models. **Results:** Lung cancer mortality was elevated among mixed beryllium (soluble and insoluble-exposed) workers hired pre-1955, but not among insoluble-only workers during any period. Other nonmalignant respiratory disease mortality was significantly elevated in the total cohort, driven by mortality among mixed-exposure facilities and among workers hired pre-1955. **Conclusions:** No increase in lung cancer or other mortality for any timeframe for workers at insoluble-only beryllium facilities was observed.

Keywords: occupational health, beryllium, mortality, epidemiology, lung cancer

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Funding sources: The results reported herein correspond to specific aims of grant # TX220306P1 awarded to investigators TAF, PB, and Dr. Constantine Dumas by the U.S. Department of Defense.
Conflicts of interest: A co-investigator on the project (Dr. Constantine Dumas) and one of the authors (GHH) are employed by Materion, a beryllium manufacturing company. Authors PB and TAF both previously consulted with Materion and Materion has provided additional financial support for the next phase of this study.
Authors' contributions: TAF and PB contributed to the funding acquisition and concept and design of the study. TAF, GHH, AMJ, and JL contributed to the project administration and data processing. TAF, AMJ, MJL, PB, and HW contributed to the data analysis and data interpretation. MJL, TAF, PB, and AMJ contributed to the manuscript preparation. All authors contributed to the critical revision of the manuscript and agreed to the final version.
Data Availability: The data that support the findings of this study are available within the article. Additional data are not publicly available due to restrictions on sharing mortality data.
EQUATOR Network Reporting: This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines.
Ethical Considerations: This study was reviewed and approved by WCG IRB #20111678.
AI Transparency and Accountability: AI technologies or models were not used utilized in any stages of the hypothesis, data collection, data evaluation, or manuscript preparation for this study.
Supplemental digital contents are available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.joem.org).
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DOI: 10.1097/JOM.0000000000003463

LEARNING OUTCOMES

- Describe patterns of mortality observed among beryllium workers, particularly focusing on lung cancer or nonmalignant respiratory disease other than chronic obstructive pulmonary disease, but also considering mortality due to all cancers, all causes, as well as other relevant neoplasms (bladder, kidney, central nervous system).
- Explain the potential impact of the solubility status of occupational beryllium exposures on the risk of mortality among beryllium workers.

Exposure to beryllium has been associated with adverse health effects in work environments that release beryllium particulate into the air. Historically, high-level exposures (>100 μg/m^3) to soluble beryllium compounds during the chemical extraction process were found to cause acute pneumonitis (acute beryllium disease, ABD) in exposed workers.[1,2] Today, ABD is a historical artifact and soluble beryllium compounds are primarily used in the primary extraction of beryllium and are not found in beryllium-containing products. Soluble beryllium products are occasionally used in scientific research projects.[3] Exposure to beryllium-containing materials at very low airborne exposure levels can cause an immunologically mediated, granulomatous pulmonary disease called chronic beryllium disease (CBD) in persons who are genetically susceptible.[2] Exposure to airborne beryllium particulate has also been associated with mortality due to lung cancer,[4] neoplasms of the central nervous system (CNS),[5–7] cancer of the kidney,[7,8] and possibly urinary tract cancer,[6] as well as with mortality from nonneoplastic respiratory diseases other than chronic obstructive pulmonary disease (COPD) and asthma (henceforth other nonmalignant respiratory diseases [ONMRD]),[9] a category that includes the International Classification of Diseases (ICD) code for berylliosis (but does not distinguish between CBD and ABD).

In 1993, the International Agency for Research on Cancer determined there was "sufficient evidence" that beryllium was a human carcinogen.[4] The evaluation was largely driven by findings concerning lung cancer in a cohort of employees from seven United States (US) beryllium manufacturing facilities.[10] A 2016 evaluation of 15 US beryllium manufacturing facilities, including the aforementioned seven facilities, reported that the risk of lung cancer and ONMRD (which includes berylliosis) increased only among workers who were first employed before 1955 (when exposure levels were very high) in facilities with soluble or mixed (soluble and insoluble) beryllium exposure, but not in workers first employed after that year in any type of beryllium facility.[9] Workers at facilities in which only insoluble forms of beryllium were utilized had no increased risk of lung cancer or ONMRD, both before and after 1955. The 2016 cohort study noted that ONMRD was chosen as a broader category of interest in the mortality analyses since a portion of mortality from beryllium disease may have been misclassified as another ONMRD disease[9] and other studies have also examined broader category groupings.[7,8]

The 2016 cohort study reported no excess mortality in beryllium workers for cancers of the CNS, bladder, and urinary tract.[9] The 2016 study also reported an excess of mortality from ONMRD, which was restricted to workers exposed to soluble beryllium.[9] However, this study lacked quantitative exposure data as well as detailed information on potential confounders, including tobacco smoking or other occupational exposures, such as acid mists or free silica. More conclusive evidence is therefore needed not only on lung cancer risk, but on several aspects of health effects potentially related to soluble versus insoluble beryllium exposures and other exposures. In addition, based on emerging evidence from previous studies, more quantitative results are needed to examine the presence or absence of an association between beryllium exposure and other neoplasms, such as CNS tumors and cancers of the urogenital tract, as well as ONMRD.[5–9]

The present study expands the 2016 cohort, and completes an update, adding 1,034 eligible workers, 11 additional years of follow-up, and 64,762 additional person-years of follow-up, improving statistical power of analyses, and to further evaluate multiple causes of death that may warrant additional monitoring based upon previous analysis of this cohort.

METHODS

This study followed the reporting guidelines recommended for observational studies (Strengthening the Reporting of Observational Studies in Epidemiology) (see Supplemental Data 1, http://links.lww.com/JOM/C3).

Cohort Enumeration

The present study updated follow-up for the cohort of workers, previously enumerated in 2016,[9] who worked at least 1 day in one of 15 beryllium manufacturing and distribution facilities operational in the US between 1925 and 2020 and expanded cohort eligibility for the existing facilities (Supplemental Table 1, http://links.lww.com/JOM/C4) through December 31, 2020, which identified an additional 1,034 workers eligible for study inclusion. Details of the cohort enumeration were reported previously.[9,11] Briefly, facilities were grouped as either insoluble or mixed facilities based on toxicological and chemical characteristics of the beryllium form used. Because of the lack of available quantitative exposure and employment history data for this analysis, beryllium facility type was used as a surrogate measure of potential beryllium exposure. Individual-level exposure to different forms of beryllium in a facility handling both insoluble and soluble forms was not determined in this analysis. As previously described in Boffetta et al (2016), a total of eight facilities (including the four distribution centers and the Reading facility during post-1965 operation) only processed insoluble forms of beryllium (Supplemental Table 1, http://links.lww.com/JOM/C4). Examples include beryllium-containing alloys (primarily in the form of copper beryllium), metallic beryllium, and beryllium oxide. A total of seven facilities, including the facility in Reading before 1965, processed soluble forms of beryllium (e.g., beryllium fluoride, chloride, phosphate, sulfate [tetrahydrate], and nitrate) in combination with insoluble forms,[9] and will be henceforth referred to as mixed facilities (Supplemental Table 1, http://links.lww.com/JOM/C4). Employment records and payroll information, as well as other data sources were used to enumerate the cohort.[9]

Person-years of observation were calculated from the first hire date through the end of the follow-up period, which was considered either the date of death or the end of the stated follow-up period (December 31, 2020). The date of birth, hire date, and date of termination were known for each new cohort member, thus no methods were needed to account for missing data in the present cohort expansion. Methods for handling missing data in the original cohort are detailed by Boffetta et al (2016).[9] The age at hire was calculated as the years between first hire date and date of birth. Employment duration was based on subtracting the last termination date from the date of first hire for workers, including combining their length of employment if they worked at multiple facilities. Consistent with the last update of this cohort, workers who had been employed in multiple facilities were included in analyses of all combined facilities for their total duration of employment and in stratified analysis of individual facilities for the length of employment specific to each facility.[9]

Follow-up

Vital status was considered through December 31, 2020. The National Center for Health Statistics' National Death Index was used to ascertain vital status. National Death Index Plus was used to determine the ICD revision applicable at time of death. Additional years of follow-up were not included in the evaluation due to the lack of availability of further mortality rates at the time the study was conducted. In the original cohort, the Pension Benefit Administration Death Audit Service, Social Security Administration, as well as searches of genealogy websites were used to ascertain vital status. Death certificates were used to obtain ICD codes.[9] A certified nosologist reviewed death certificates and then coded the underlying cause of death to the ICD revision in effect at the time of death. For workers whose vital status was unknown at the end of the study, the end of follow-up was defined as 1 year after their date of termination. Employees who were born prior to 1921 whose vital status was not coded as dead were considered lost to follow-up and had their cause of death coded as unknown. Employees with a known date of death but an unknown cause of death were considered lost to follow-up. Overall, 693 cohort members (4%) were lost to follow-up. Workers who were not lost to follow-up and not found to be deceased were presumed to be alive at the end of the study period. Race was unknown for the majority of the cohort (~70%) and was weighted in analyses based on cohort members with known race. Results displayed contain race weighting.

Statistical Analysis

Standardized mortality ratios (SMRs) and 95% confidence intervals (95% CIs) were calculated using the Occupational Cohort Mortality Analysis Program, developed by the University of Pittsburgh, as the ratio of observed deaths compared to expected deaths.[12] Expected deaths were calculated using US mortality rates obtained from a combination of data provided by the University of Pittsburgh's Mortality and Population Data System and data published by the US Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) online database.[13] State rates were not utilized for analysis due to the National Center for Health Statistics requirement to suppress cause of death counts less than 10, which would lead to the suppression of multiple results evaluated in subanalyses, potentially resulting in underestimation of SMRs.

Summary statistics by sex, race/ethnicity, birth year, year of hire, employment duration, and time since hire for the total cohort and for specific cause of death categories by beryllium facility type were calculated. A total of 64 causes of death were evaluated in SMR analysis for the total cohort and by subcategories such as beryllium facility type, sex, length of employment, and period of hire. SMRs were additionally calculated for subanalyses of *a priori* causes of death of interest, including potential mesothelioma, COPD, lung cancer, ONMRD (which contains berylliosis, as defined in Supplemental Table 2, http://links.lww.com/JOM/C5), all cancers, kidney cancer, bladder cancer, and cancer of the CNS. These analyses were stratified by year of hire, employment duration, time since hire, and beryllium facility type for the total cohort. SMRs were also calculated by facility for select causes of death. Additional analyses were conducted for some selected outcomes where overall analysis showed statistically significant elevation to further evaluate characteristics of subpopulations, such as short-term workers (workers employed less than 1 year).

Another subanalysis was conducted to calculate SMRs for potential mesothelioma by beryllium facility type and further stratified by year of hire, length of employment, and time since hire. Deaths due to mesothelioma were defined by utilizing ICD-10 mesothelioma-specific codes for deaths occurring in 1999 or later. Because mesothelioma-specific codes did not exist prior to 1999, mesothelioma deaths could not be definitively identified during this time period; however, we utilized ICD codes that could encompass potential mesothelioma deaths in the revision used at the time of death, determined by a certified nosologist. This process has been described in greater detail previously.[14] Thus, potential mesothelioma deaths are likely overcounted in this analysis as other diseases are included for ICD revisions prior to ICD-10 and the misclassification may result in biasing results toward the null.

Cox regression models, adjusted for age at hire and other potential confounding exposure variables, were implemented to estimate hazard ratios (HRs) and 95% CIs. The proportional hazards assumption was tested for mortality from *a priori* causes of death (all-cause mortality, all cancers, lung cancer, kidney cancer, bladder cancer, CNS, and ONMRD) using a graphical approach.[15] Using this method, the log-log survival curves over different levels of the categorical variables (employment duration, hire period, sex, and beryllium facility type) are plotted and assessed to determine that the curves appear reasonably parallel (i.e., they do not cross each other). A crossing of these curves would indicate that the proportional hazards assumption was violated. Age at hire was included as a continuous variable in the model. Consistent with previous analyses of this cohort,[9] employment duration was analyzed separately as both a dichotomous variable (<1 year vs 1+ years) and as a continuous variable. Period of hire was also considered as both a dichotomous variable (before 1955 vs 1955 and later) and continuous in separate models. Type of beryllium facility was categorized as a dichotomous variable (mixed vs insoluble beryllium), where workers who had been employed in both insoluble only and mixed facilities were categorized under mixed beryllium facility. The final fitted Cox regression models for mortality from *a priori* causes of death included sex, age at hire (continuous), employment duration (<1 year vs 1+ years), period of hire (before 1955 vs 1955 and later), and type of beryllium facility. The models did not consider race as most workers either had unknown race or were White. Time on study was used to define event time (time to death, end of study follow-up, or loss to follow-up). Regression models were fit with and without interaction terms. The interaction terms included were based on statistically significant interactions identified in the all-cause mortality model with significance assessed at an $\alpha = 0.05$. As a sensitivity analysis, Cox models were also performed incorporating a 10-year lag period into the primary regression models. An additional sensitivity analysis was performed, by considering cases of mortality due to berylliosis (ICD-10: J63.2, ICD-9: 503, ICD-8: 516.0, ICD-7 and ICD-6: 524, and ICD-5: 114b) in a separate Cox model and comparing findings to the model of ONMRD.

Tests for trend were conducted using the Breslow-Day method to examine if there were any dose-response trends as a function of duration of employment and time since hire.[16] SAS software version 9.4 (Copyright © 2016 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA) was used for Cox regression models and trend tests.

RESULTS

The current study identified 1,034 additional workers who were eligible for study inclusion and 64,762 additional person-years of follow-up, for a total cohort comprised of 17,149 workers and 632,726 person-years of follow-up. Members of the cohort were primarily White (95.8%), male (83.4%), hired in 1955 or after, and employed for less than 5 years (68%) (Table 1). A total of 9,717 deaths occurred by the end of study follow-up.

Total Cohort Analysis With Beryllium Facility Type Stratification

The risk of mortality for all causes of death among the total cohort compared to the US population was not elevated (SMR: 1.01; 95% CI: 0.99–1.03) (Table 2). When evaluated by beryllium facility type, the SMR for all causes of death was elevated for mixed facilities (SMR: 1.06; 95% CI: 1.04–1.09), but not elevated for insoluble

TABLE 1. Selected Characteristics by Beryllium Facility Type

	Mixed Beryllium Facilities		Insoluble Beryllium Facilities		Total Cohort	
	n at Risk	Person-Years (%)	*n* at Risk	Person-Years (%)	*n* at Risk	Person-Years (%)
Overall	11,011	414,699.2	6,138	218,026.4	17,149	632,725.6
Sex						
Male	9,567	362,663.6 (87)	4,742	167,722.7 (76)	14,309	530,386.3 (84)
Female	1,444	52,035.5 (13)	1,396	50,303.8 (23)	2840	102,339.3 (16)
Race/ethnicity						
White	10,700	403,845.8 (97)	5,819	205,376.9 (94)	16,426	605,156.5 (96)
Non-White	312	10,853.3 (3)	319	12,649.6 (6)	723	27,569.1 (4)
Year of birth						
<1920	3,292	103,147.9 (25)	637	19,348.4 (9)	3,929	122,496.2 (19)
1920–1939	4,195	209,049.2 (50)	1,742	77,792.2 (36)	5,937	286,841.4 (45)
1940–1959	1,918	76,242.2 (18)	2,303	85,885.0 (39)	4,221	162,127.1 (26)
1960+	1,606	26,259.9 (6)	1,456	35,000.9 (16)	3,062	61,260.8 (10)
Year of hire						
<1955	5,236	214,152.7 (52)	768	33,717.2 (15)	6,004	247,869.9 (39)
1955+	5,775	200,546.4 (48)	5,370	184,309.3 (85)	11,145	384,855.7 (61)
Duration of employment						
<5 yrs	11,011	291,085.3 (70)	6,138	157,558.2 (72)	17,149	448,643.6 (71)
5–14 yrs	3,622	72,339.3 (17)	1,930	40,023.4 (18)	5,552	112,362.7 (18)
15–29 yrs	1,794	34,811.2 (8)	807	16,739.8 (8)	2,601	51,551.0 (8)
30+ yrs	807	16,463.3 (4)	226	3,705.0 (2)	1,033	20,168.3 (3)
Time since hire						
<10 yrs	11,011	102,482.5 (25)	6,138	59,464.8 (27)	17,149	161,947.3 (26)
10–19 yrs	9,715	92,983.9 (22)	5,764	55,075.9 (25)	15,479	148,059.8 (23)
20–29 yrs	8,889	79,990.5 (19)	5,185	45,786.3 (21)	14,074	125,776.8 (20)
30+ yrs	7,338	139,242.2 (34)	4,074	57,699.5 (26)	11,412	196,941.7 (31)

Percentages may not sum to 100 due to rounding.

TABLE 2. Standardized Mortality Ratios for Causes of Death, by Beryllium Facility Type

	Mixed Beryllium				Insoluble Beryllium				Total Cohort			
Cause of Death	**Obs**	**Exp**	**SMR**	**95% CI**	**Obs**	**Exp**	**SMR**	**95% CI**	**Obs**	**Exp**	**SMR**	**95% CI**
All causes of death	7177	6746.2	1.06**	1.04–1.09	2540	2843.4	0.89**	0.86–0.93	9717	9602.2	1.01	0.99–1.03
Tuberculosis	14	7.5	1.86*	1.02–3.12	1	2.3	0.43	0.01–2.39	15	10.1	1.49	0.83–2.45
All malignant neoplasms	1646	1688.6	0.98	0.93–1.02	673	718.4	0.94	0.87–1.01	2319	2410.1	0.96	0.92–1.00
Cancer of buccal cavity & pharynx	37	34.6	1.07	0.75–1.47	12	14.2	0.85	0.44–1.48	49	49.0	1.00	0.74–1.32
Cancer of digestive organs & peritoneum	381	423.1	0.90*	0.81–0.996	172	177.0	0.97	0.83–1.13	553	601.4	0.92*	0.85–1.00
Cancer of esophagus	48	46.3	1.04	0.76–1.37	25	21.1	1.19	0.77–1.75	73	67.7	1.08	0.85–1.36
Cancer of stomach	43	52.2	0.82	0.60–1.11	15	18.0	0.84	0.47–1.38	58	70.6	0.82	0.62–1.06
Cancer of large intestine	144	139.6	1.03	0.87–1.21	61	55.3	1.10	0.84–1.42	205	195.0	1.05	0.91–1.21
Cancer of rectum	25	31.0	0.81	0.52–1.19	13	11.3	1.16	0.62–1.98	38	42.2	0.90	0.64–1.24
Cancer of biliary passages & liver	26	45.9	0.57**	0.37–0.83	19	23.4	0.81	0.49–1.27	45	69.6	0.65**	0.47–0.87
Cancer of pancreas	80	90.9	0.88	0.70–1.10	35	40.6	0.86	0.60–1.20	115	131.6	0.87	0.72–1.05
Cancer of all other digestive organs	15	17.2	0.87	0.49–1.44	4	7.5	0.54	0.15–1.37	19	24.7	0.77	0.46–1.20
Cancer of respiratory system	606	545.1	1.11*	1.03–1.20	208	230.4	0.90	0.78–1.03	814	776.9	1.05	0.98–1.12
Cancer of larynx	16	17.6	0.91	0.52–1.48	4	7.0	0.57	0.16–1.47	20	24.7	0.81	0.49–1.25
Cancer of bronchus, trachea, lung	582	522.8	1.11*	1.03–1.21	201	221.7	0.91	0.79–1.04	783	745.7	1.05	0.98–1.13
Cancer of all other respiratory	8	4.7	1.71	0.74–3.37	3	1.8	1.68	0.35–4.89	11	6.5	1.70	0.85–3.04
Cancer of breast	20	28.9	0.69	0.42–1.07	21	20.4	1.03	0.64–1.57	41	49.3	0.83	0.60–1.13
All uterine cancers (females only)	5	8.3	0.60	0.20–1.41	10	5.6	1.80	0.86–3.30	15	13.7	1.10	0.61–1.81
Cancer of cervix uteri (females only)	1	3.6	0.28	0.01–1.55	3	2.3	1.33	0.27–3.88	4	5.8	0.69	0.19–1.78
Cancer of other female genital organs	6	10.0	0.60	0.22–1.31	8	7.3	1.10	0.47–2.17	14	17.4	0.81	0.44–1.35
Cancer of prostate (males only)	138	152.5	0.91	0.76–1.07	53	55.2	0.96	0.72–1.26	191	208.9	0.92	0.79–1.05
Cancer of testes and other male genital organs	5	4.3	1.16	0.38–2.70	1	1.5	0.65	0.02–3.60	6	5.8	1.03	0.38–2.24
Cancer of kidney	34	41.5	0.82	0.57–1.15	20	18.1	1.11	0.68–1.71	54	59.5	0.91	0.68–1.18
Cancer of bladder and other urinary organs	61	55.4	1.10	0.84–1.41	20	21.4	0.94	0.57–1.44	81	76.6	1.06	0.84–1.31
Malignant melanoma of skin	17	26.1	0.65	0.38–1.04	11	12.2	0.90	0.45–1.61	28	38.1	0.74	0.49–1.06
Cancer of eye	2	1.0	1.99	0.24–7.20	0	0.4	—	—	2	1.4	1.44	0.17–5.20
Cancer of central nervous system	34	40.0	0.85	0.59–1.19	17	18.7	0.91	0.53–1.46	51	58.5	0.87	0.65–1.15
Cancer of thyroid & other endocrine glands	5	5.3	0.94	0.31–2.20	2	2.4	0.85	0.1–3.07	7	7.6	0.92	0.37–1.89
Cancer of bone	8	4.3	1.85	0.80–3.65	2	1.6	1.25	0.15–4.51	10	5.9	1.69	0.81–3.11
Cancer of all lymphatic, hematopoietic tissue	140	169.5	0.83*	0.70–0.98	64	71.1	0.90	0.69–1.15	204	240.4	0.85*	0.74–0.97
Hodgkins disease	6	8.2	0.73	0.27–1.60	2	2.8	0.72	0.09–2.61	8	10.9	0.73	0.32–1.44
Non-Hodgkins lymphoma	64	62.2	1.03	0.79–1.31	28	26.7	1.05	0.70–1.52	92	88.7	1.04	0.84–1.27
Leukemia and aleukemia	51	67.8	0.75*	0.56–0.99	20	28.0	0.71	0.44–1.10	71	95.6	0.74*	0.58–0.94
Cancer of all other lymphopoietic tissue	19	31.2	0.61*	0.37–0.95	14	13.6	1.03	0.56–1.72	33	45.0	0.73	0.51–1.03
All other malignant neoplasms	147	138.7	1.06	0.90–1.25	52	60.8	0.86	0.64–1.12	199	199.6	0.997	0.86–1.15
Benign neoplasms	19	12.0	1.58	0.95–2.47	4	4.3	0.92	0.25–2.36	23	16.4	1.41	0.89–2.11
diabetes mellitus	139	151.9	0.92	0.77–1.08	63	72.1	0.87	0.67–1.12	202	224.6	0.90	0.78–1.03
Cerebrovascular disease	365	392.3	0.93	0.84–1.03	105	145.4	0.72**	0.59–0.87	470	539.2	0.87**	0.8–0.95
All heart disease	2254	2280.5	0.99	0.95–1.03	766	855.1	0.90**	0.83–0.96	3020	3136.3	0.96*	0.93–1.00
Rheumatic heart disease	13	21.6	0.60	0.32–1.03	6	7.1	0.84	0.31–1.83	19	28.7	0.66	0.40–1.03
Ischemic heart disease	1693	1706.9	0.99	0.95–1.04	552	612.0	0.90*	0.83–0.98	2245	2317.6	0.97	0.93–1.01
Chronic endocard. dis; other myocard. insuff.	79	82.1	0.96	0.76–1.20	40	30.7	1.30	0.93–1.77	119	112.8	1.06	0.87–1.26
Hypertension with heart disease	55	73.6	0.75*	0.56–0.97	29	34.2	0.85	0.57–1.22	84	108.7	0.77*	0.62–0.96
All other heart disease	414	396.2	1.05	0.95–1.15	139	171.0	0.81*	0.68–0.96	553	568.3	0.97	0.89–1.06
Hypertension w/o heart disease	43	41.6	1.03	0.75–1.39	17	19.6	0.87	0.51–1.39	60	61.6	0.97	0.74–1.25
Nonmalignant respiratory disease	684	631.2	1.08*	1.00–1.17	228	261.1	0.87*	0.76–0.99	912	892.6	1.02	0.96–1.09
Influenza & pneumonia	131	171.9	0.76**	0.64–0.90	43	63.6	0.68**	0.49–0.91	174	236.1	0.74**	0.63–0.86
Bronchitis, emphysema, asthma	257	249.8	1.03	0.91–1.16	91	117.0	0.78*	0.63–0.96	348	366.6	0.95	0.85–1.06
Bronchitis	191	181.3	1.05	0.91–1.21	69	93.2	0.74*	0.58–0.94	260	274.3	0.95	0.84–1.07
Emphysema	61	60.9	1.00	0.77–1.29	19	20.3	0.93	0.56–1.46	80	81.1	0.99	0.78–1.23
Asthma	5	7.7	0.65	0.21–1.52	3	3.4	0.88	0.18–2.56	8	11.2	0.72	0.31–1.41
Other nonmalignant respiratory disease	296	231.4	1.28**	1.14–1.43	94	95.7	0.98	0.79–1.20	390	327.1	1.19**	1.08–1.32
Ulcer of stomach & duodenum	15	19.0	0.79	0.44–1.30	4	6.2	0.64	0.17–1.64	19	25.3	0.75	0.45–1.17
Cirrhosis of liver	82	106.4	0.77*	0.61–0.96	41	51.6	0.80	0.57–1.08	123	158.5	0.78**	0.65–0.93
Nephritis & nephrosis	97	91.7	1.06	0.86–1.29	32	41.8	0.77	0.52–1.08	129	133.9	0.96	0.81–1.15
All external causes of death	323	375.9	0.86**	0.77–0.96	167	199.9	0.84*	0.71–0.97	490	578.4	0.85**	0.77–0.93
Accidents	233	251.1	0.93	0.81–1.06	98	128.3	0.76**	0.62–0.93	331	380.3	0.87*	0.78–0.97
Motor vehicle accidents	86	93.5	0.92	0.74–1.14	39	49.6	0.79	0.56–1.08	125	143.4	0.87	0.73–1.04
All other accidents	147	157.6	0.93	0.79–1.10	59	78.7	0.75*	0.57–0.97	206	236.9	0.87*	0.76–1.00
Suicides	79	89.3	0.89	0.70–1.10	54	47.5	1.14	0.85–1.48	133	136.2	0.98	0.82–1.16
Homicides & other external causes	11	35.5	0.31**	0.16–0.55	15	24.1	0.62	0.35–1.03	26	61.9	0.42**	0.27–0.62
All other causes of death	882	1007.4	0.88**	0.82–0.94	354	457.3	0.77**	0.70–0.86	1236	1466.1	0.84**	0.80–0.89
AIDS	2	12.0	0.17**	0.02–0.60	4	13.2	0.30**	0.08–0.78	6	25.9	0.23**	0.09–0.50
Unknown causes (in all causes category only)	612	—	—	—	81	–	—	—	693	—	—	—

CI, confidence interval; Exp, expected deaths, based on national reference rates; Obs, observed deaths; SMR, standardized mortality ratio.
*$P < 0.05$.
**$P < 0.01$.

facilities (SMR: 0.89; 95% CI: 0.86–0.93). There was only one cause of death that was elevated for the total cohort, ONMRD (SMR: 1.19; 95% CI: 1.08–1.32). There were no significantly elevated SMRs among insoluble facility workers for any cause of death, including ONMRD (Table 2). Multiple causes of death were elevated among mixed facility workers, specifically in respiratory-related categories, including tuberculosis based upon 14 observed deaths (SMR: 1.86; 95% CI: 1.02–3.12), respiratory system cancer (SMR: 1.11; 95% CI: 1.03–1.20), and the subcategory cancer of the lung (SMR: 1.11; 95% CI: 1.03–1.21). Both nonmalignant respiratory disease and ONMRD were elevated for mixed beryllium facilities (SMR: 1.08; 95% CI: 1.00–1.17 and SMR: 1.28; 95% CI: 1.14–1.43, respectively).

Total Cohort Analysis Stratified by Sex

When evaluated by sex, similar results were observed as were reported for the total cohort with a few statistically significant SMRs (Supplementary Table 3, http://links.lww.com/JOM/C6). Benign neoplasms were elevated for male workers (SMR: 1.61; 95% CI: 1.02–2.42) based on 23 deaths, while there were no deaths due to benign neoplasms observed among female workers. Cancer of bone was elevated among the 2,840 female workers based upon three deaths (SMR: 5.24; 95% CI: 1.08–15.32). ONMRD was elevated among both male workers (SMR: 1.17; 95% CI: 1.05–1.30) and female workers (SMR: 1.39; 95% CI: 1.03–1.84).

Length of Employment Analysis

There were no elevated SMRs for workers employed for one or more years among the total cohort and among workers at insoluble facilities (Supplemental Table 4, http://links.lww.com/JOM/C7). The category benign neoplasms was elevated for workers in mixed facilities with a length of employment greater than 1 year (SMR: 1.94; 95% CI: 1.00–3.39) based upon 12 deaths. ONMRD was also elevated in this subgroup of workers (SMR: 1.34; 95% CI: 1.14–1.56).

Sensitivity analyses of short-term workers (employed less than 1 year), further stratified length of employment into subcategories (less than 1 month, less than 3 months, less than 1 years). There were multiple elevated SMRs for short-term workers at mixed beryllium facilities (Supplemental Table 5, http://links.lww.com/JOM/C8). All causes of death were elevated for all three subcategories of length of employment evaluated among short-term mixed beryllium facility workers (SMR range 1.16–1.25). Cancer of the respiratory system and subcategory of cancer of lung were elevated in each length of employment subgroup (SMR range: 1.20–1.34 and SMR range: 1.19–1.34, respectively). All heart disease and subcategory ischemic heart disease were elevated for all three length of employment subgroups (SMR range: 1.07–1.14 and SMR range: 1.08–1.16, respectively). Cause of death category, asthma, was also elevated across the three subcategories (SMR range: 1.21–1.41). Cancer of the bone was elevated for mixed facility workers employed for less than 1 month based upon four deaths (SMR: 5.38; 95% CI: 1.47–13.73). Nonmalignant respiratory diseases were elevated for mixed facility workers with a length of employment of less than 1 month (SMR: 1.24; 95% CI: 1.04–1.48). ONMRD was elevated for mixed facility workers with a length of employment of less than 1 year (SMR: 1.21; 95% CI: 1.01–1.44). Bronchitis was elevated for mixed facility workers with a length of employment of less than 1 month and less than 3 months (SMR: 1.51; 95% CI: 1.06–2.09 and SMR: 1.35; 95% CI: 1.02–1.75, respectively).

Period of Hire Analysis

Period of hire category results among workers hired pre-1955 and 1955 and later for insoluble facility workers and the total cohort were generally similar (data not shown). Only one cause of death was elevated, chronic endocarditis; other myocardial insufficiency, in workers hired after 1955 (SMR: 1.53; 95% CI: 1.05–2.17). There were differences in elevated causes of death by period of hire among mixed beryllium facility workers (Table 3). No causes of death were elevated among workers hired 1955 and later who worked in mixed beryllium facilities (Table 3). In contrast, multiple causes of death were elevated among mixed beryllium facility workers hired prior to 1955, resulting in an elevated SMR for all causes of death (SMR: 1.21; 95% CI: 1.17–1.24). Similar to the overall analysis among mixed beryllium facility workers, tuberculosis, cancer of respiratory system, and subcategory cancer of lung, as well as cancer of bone, all heart diseases, nonmalignant respiratory diseases, and ONMRD were elevated (Table 3). Additional categories, including bronchitis, emphysema, and asthma (SMR: 1.28; 95% CI: 1.09–1.148); the subcategory bronchitis (SMR: 1.35; 95% CI: 1.11–1.61); and all other heart disease (SMR: 1.22; 95% CI: 1.08–1.36) were elevated among those hired before 1955 in mixed beryllium facilities compared to the US population.

Individual Facility Analysis for Select Causes of Death

When evaluated by facility, there were no elevated SMRs for all cancers (Supplemental Table 6, http://links.lww.com/JOM/C9). SMRs for Lorain (operational prior to 1950) and Reading prior to 1965 (both mixed facilities) were elevated for lung cancer (SMR: 1.42; 95% CI: 1.20–1.68 and SMR: 1.22; 95% CI: 1.08–1.39, respectively). SMRs of ONMRD evaluated among workers at multiple mixed facilities including Elmore, Hazleton, Lorain, and Reading first hire prior to 1965 were elevated (SMR range: 1.26–1.60) (Supplemental Table 6, http://links.lww.com/JOM/C9). There were no elevated SMRs by individual facility for either kidney cancer or CNS cancer (Supplemental Table 7, http://links.lww.com/JOM/C10). Bladder cancer was elevated among Elmore (mixed facility) workers compared to the US population, based on 19 observed deaths (SMR: 1.71; 95% CI: 1.03–2.67).

Additional Analyses for Select Causes of Death

Potential Mesothelioma

There were no elevated SMRs among the total cohort or by facility type for potential mesothelioma by hire year, time since hire, or duration of employment (Supplemental Table 8, http://links.lww.com/JOM/C11). Of the 70 deaths observed in the cohort attributed to potential mesothelioma, 17 occurred on or after 1999 (24%), under ICD-10, when a specific code for mesothelioma was first introduced (ICD-10: 45.0–45.9). The majority of cases occurred among workers who had been hired 30+ years ago and had been employed for less than 5 years. The expected number of deaths due to mesothelioma under ICD-10 was 21.

Chronic Obstructive Pulmonary Disease

Mixed beryllium workers had an elevated SMR for COPD among those hired pre-1955 (SMR: 1.29; 95% CI: 1.10–1.49). This association was not elevated among mixed facility workers hired in 1955 and later (SMR 0.77; 95% CI: 0.61–0.96), and not significant over any time period for insoluble beryllium workers. The SMR for COPD among all workers hired pre-1955 was elevated, but appeared to be driven by the mixed workers (Supplemental Table 8, http://links.lww.com/JOM/C11). The SMR for COPD among the total cohort across all time periods was nonsignificant (SMR: 0.99; 95% CI: 0.89–1.10). Nonsignificant SMRs for COPD were also observed in stratified analyses of employment duration and time since hire.

Lung Cancer

Mixed beryllium workers had an SMR elevated for those hired pre-1955 (SMR: 1.27; 95% CI: 1.15–1.40) but not among those hired in 1955 and later (SMR: 0.88; 95% CI: 0.76–1.02) ($P < 0.001$) (Supplemental Table 8, http://links.lww.com/JOM/C11). The SMRs among workers hired at insoluble only facilities during any time period were not elevated (SMR: 0.91; 95% CI: 0.79–1.04). Of 15 facilities,

TABLE 3. Standardized Mortality Ratios for Causes of Death, Among Workers of Mixed Beryllium Facilities, by Period of Hire

	Pre 1955				1955 and Later			
Cause of Death	**Obs**	**Exp**	**SMR**	**95% CI**	**Obs**	**Exp**	**SMR**	**95% CI**
All causes of death	4996	4141.9	1.21**	1.17–1.24	2181	2605.1	0.84**	0.8–0.87
Tuberculosis	14	5.9	2.36**	1.29–3.96	0	1.6	—	—
All malignant neoplasms	1041	1014.0	1.03	0.97–1.09	605	675.0	0.90**	0.83–0.97
Cancer of buccal cavity & pharynx	24	21.3	1.13	0.72–1.67	13	13.3	0.98	0.52–1.67
Cancer of digestive organs & peritoneum	235	257.6	0.91	0.8–1.04	146	165.6	0.88	0.74–1.04
Cancer of esophagus	26	24.9	1.04	0.68–1.53	22	21.4	1.03	0.65–1.56
Cancer of stomach	24	36.7	0.65*	0.42–0.97	19	15.6	1.22	0.74–1.91
Cancer of large intestine	93	89.4	1.04	0.84–1.28	51	50.2	1.02	0.76–1.34
Cancer of rectum	21	21.0	1.00	0.62–1.53	4	10.0	0.4	0.11–1.03
Cancer of biliary passages & liver	18	23.2	0.77	0.46–1.22	8	22.7	0.35**	0.15–0.69
Cancer of pancreas	43	52.1	0.83	0.6–1.11	37	38.8	0.95	0.67–1.31
Cancer of all other digestive organs	10	10.2	0.98	0.47–1.8	5	6.9	0.72	0.23–1.68
Cancer of respiratory system	409	323.2	1.27**	1.15–1.39	197	222.0	0.89	0.77–1.02
Cancer of larynx	9	11.0	0.82	0.37–1.55	7	6.6	1.06	0.42–2.18
Cancer of bronchus, trachea, lung	393	309.2	1.27**	1.15–1.4	189	213.7	0.88	0.76–1.02
Cancer of all other respiratory	7	3.0	2.30	0.92–4.74	1	1.6	0.61	0.02–3.41
Cancer of breast	9	16.7	0.54	0.25–1.03	11	12.2	0.9	0.45–1.61
All uterine cancers (females only)	3	4.9	0.61	0.13–1.77	2	3.3	0.6	0.07–2.16
Cancer of cervix uteri (females only)	0	2.3	—	—	1	1.3	0.75	0.02–4.16
Cancer of other female genital organs	4	5.8	0.69	0.19–1.76	2	4.2	0.48	0.06–1.73
Cancer of prostate (males only)	94	101.8	0.92	0.75–1.13	44	51.0	0.86	0.63–1.16
Cancer of testes and other male genital organs	3	2.7	1.11	0.23–3.24	2	1.6	1.24	0.15–4.47
Cancer of kidney	24	23.5	1.02	0.65–1.52	10	18.0	0.56	0.27–1.02
Cancer of bladder and other urinary organs	37	34.4	1.08	0.76–1.48	24	21.0	1.14	0.73–1.7
Malignant melanoma of skin	10	13.4	0.75	0.36–1.38	7	12.7	0.55	0.22–1.14
Cancer of eye	2	0.6	3.13	0.38–11.31	0	0.4	—	—
Cancer of central nervous system	15	21.8	0.69	0.39–1.13	19	18.2	1.04	0.63–1.63
Cancer of thyroid & other endocrine glands	3	3.1	0.98	0.2–2.86	2	2.2	0.9	0.11–3.24
Cancer of bone	8	2.9	2.80*	1.21–5.52	0	1.5	—	—
Cancer of all lymphatic, hematopoietic tissue	74	100.2	0.74**	0.58–0.93	66	69.3	0.95	0.74–1.21
Hodgkins disease	4	5.6	0.72	0.2–1.84	2	2.6	0.77	0.09–2.79
Non-Hodgkins lymphoma	30	36.0	0.83	0.56–1.19	34	26.1	1.3	0.9–1.82
Leukemia & aleukemia	31	40.4	0.77	0.52–1.09	20	27.3	0.73	0.45–1.13
Cancer of all other lymphopoietic tissue	9	18.1	0.50*	0.23–0.95	10	13.2	0.76	0.36–1.4
All other malignant neoplasms	87	80.2	1.09	0.87–1.34	60	58.5	1.03	0.78–1.32
Benign neoplasms	13	8.3	1.57	0.83–2.68	6	3.7	1.62	0.6–3.54
Diabetes mellitus	88	83.2	1.06	0.85–1.3	51	68.8	0.74*	0.55–0.97
Cerebrovascular disease	276	270.2	1.02	0.9–1.15	89	122.3	0.73*	0.59–0.9
All heart disease	1625	1522.0	1.07**	1.02–1.12	629	758.4	0.83**	0.77–0.9
Rheumatic heart disease	10	15.8	0.63	0.30–1.16	3	5.8	0.52	0.11–1.51
Ischemic heart disease	1229	1166.9	1.05	0.995–1.11	464	539.6	0.86**	0.78–0.94
Chronic endocard. dis; other myocard. insuff.	59	55.9	1.06	0.80–1.36	20	26.2	0.76	0.47–1.18
Hypertension with heart disease	36	43.9	0.82	0.57–1.14	19	29.8	0.64*	0.38–0.99
All other heart disease	291	239.4	1.22**	1.08–1.36	123	157.0	0.78**	0.65–0.94
Hypertension w/o heart disease	29	24.2	1.20	0.8–1.72	14	17.5	0.8	0.44–1.34
Nonmalignant respiratory disease	470	390.3	1.20**	1.1–1.32	214	240.6	0.89	0.77–1.02
Influenza & pneumonia	101	118.4	0.85	0.7–1.04	30	53.5	0.56**	0.38–0.8
Bronchitis, emphysema, asthma	172	134.6	1.28**	1.09–1.48	85	115.0	0.74**	0.59–0.91
Bronchitis	116	86.3	1.35**	1.11–1.61	75	94.8	0.79*	0.62–0.99
Emphysema	52	43.4	1.20	0.89–1.57	9	17.4	0.52*	0.24–0.98
Asthma	4	4.9	0.81	0.22–2.08	1	2.7	0.36	0.01–2.03
Other nonmalignant respiratory disease	197	143.2	1.38**	1.19–1.58	99	88.1	1.12	0.91–1.37
Ulcer of stomach & duodenum	10	13.9	0.72	0.35–1.32	5	5.1	0.98	0.32–2.29
Cirrhosis of liver	51	57.8	0.88	0.66–1.16	31	48.7	0.64**	0.43–0.9
Nephritis & nephrosis	58	52.6	1.10	0.84–1.43	39	39.2	0.996	0.71–1.36
All external causes of death	202	181.1	1.12	0.97–1.28	121	194.9	0.62**	0.52–0.74
Accidents	148	125.5	1.18	0.997–1.39	85	125.7	0.68**	0.54–0.84
Motor vehicle accidents	48	42.8	1.12	0.83–1.49	38	50.7	0.75	0.53–1.03
All other accidents	100	82.7	1.21	0.98–1.47	47	75.0	0.63**	0.46–0.83
Suicides	49	41.6	1.18	0.87–1.56	30	47.6	0.63**	0.43–0.9
Homicides & other external causes	5	14.0	0.36*	0.12–0.83	6	21.7	0.28**	0.1–0.6
All other causes of death	572	588.8	0.97	0.89–1.06	310	418.7	0.74**	0.66–0.83
AIDS	0	1.2	—	—	2	10.8	0.19**	0.02–0.67
Unknown causes (in all causes category only)	547	—	—	—	65	—	—	—

CI, confidence interval; Exp, expected deaths, based on national reference rates; Obs, observed deaths; SMR, standardized mortality ratio.
*$P < 0.05$.
**$P < 0.01$.

TABLE 4. Hazard Ratios and 95% Confidence Intervals of Overall Mortality, All Cancers, Lung cancer, or ONMRD According to Sex, Age at Hire, Employment Duration, Period of Hire, and Type of Beryllium Plant

	Hazard Ratio (95% CI)			
Factor	**All Cause of Death**	**All Cancer**	**Lung Cancer**	**ONMRD**
Sex (male vs female)	1.57 (1.47–1.68)	1.67 (1.46–1.91)	2.45 (1.86–3.23)	1.25 (0.93–1.69)
Age at hire (1-year increase)	1.089 (1.087–1.092)	1.070 (1.065–1.074)	1.067 (1.059–1.076)	1.097 (1.085–1.109)
Employment duration (1+ year vs <1 year)	0.97 (0.93–1.01)	1.00 (0.92–1.09)	1.03 (0.89–1.20)	1.25 (1.01–1.56)
Period of hire (1955 or later vs before 1955)	0.63 (0.60–0.66)	0.76 (0.69–0.84)	0.65 (0.55–0.76)	0.61 (0.49–0.77)
Type of beryllium plant (mixed vs insoluble)	1.05 (1.00–1.10)	0.97 (0.88–1.06)	1.08 (0.91–1.27)	1.20 (0.94–1.53)

CI, confidence interval; ONMRD, other nonmalignant respiratory disease.

only two, Lorain and Reading pre-1965, both mixed facilities, had elevated SMRs (Supplemental Table 6, http://links.lww.com/JOM/C9). SMRs for lung cancer were not significantly elevated in analyses stratified by duration of employment except for mixed beryllium workers with <5 years employment (SMR: 1.17; 95% CI: 1.05–1.28) (Supplemental Table 8, http://links.lww.com/JOM/C11). SMRs for lung cancer were not elevated when stratified by time since hire, except for mixed beryllium workers who had been hired 30+ years ago.

All Cancers

SMRs for all cancers were not elevated among all workers hired 1955 and later (total cohort, insoluble, and mixed). Although higher SMRs were seen among workers hired prior to 1955, none were significant. These differences by period of hire were statistically significant (Supplemental Table 8, http://links.lww.com/JOM/C11). When stratified by duration of employment, significantly elevated SMRs were not seen. By time since hire, an elevated SMR for all cancers was observed among mixed beryllium workers with a time since hire of 30+ years (SMR 1.07; 95% CI: 1.02–1.13).

Kidney Cancer

There were no elevated SMRs for kidney cancer by beryllium facility type or for the total cohort (Supplemental Table 8, http://links.lww.com/JOM/C11).

Bladder Cancer

There were no elevated SMRs for bladder cancer by beryllium facility type or for the total cohort (Supplemental Table 8, http://links.lww.com/JOM/C11).

Cancer of Central Nervous System

There were no elevated SMRs for cancer of the CNS for either beryllium facility type evaluated or for the total cohort by year of hire category. (Supplemental Table 8, http://links.lww.com/JOM/C11). Significantly elevated SMRs were not seen when stratified by time since hire or duration of employment.

ONMRD

Mixed beryllium workers had an SMR elevated among those hired pre-1955 (SMR: 1.38; 95% CI: 1.19–1.58). Insoluble beryllium workers hired prior to 1955 did not have an elevated SMR for ONMRD (SMR: 1.05; 95% CI: 0.69–1.53). The SMR for ONMRD in those hired prior to 1955 was elevated among the total cohort, driven by workers at mixed beryllium facilities (Supplemental Table 8, http://links.lww.com/JOM/C11). SMRs were elevated for duration of employment of 15–29 years of employment and 30+ years of employment among both mixed facility workers and the total cohort (Supplemental Table 8, http://links.lww.com/JOM/C11). By time since hire, elevated SMRs for ONMRD were observed among workers at mixed beryllium facilities who had been hired 30+ years ago (SMR: 1.30; 95% CI: 1.14–1.47), which appeared to drive the similar association seen among the total cohort.

Cox Proportional Hazards Analysis

Upon review of the survival curves and log-log survival curves, checking the proportional hazards assumption generally yielded parallel curves for the factors with no gross violations of the proportional hazards assumption. Thus, nonstratified models are presented here. To investigate the association between exposure and mortality from all cancers, all-cause mortality, bladder cancer, lung cancer, kidney cancer, cancer of CNS, and ONMRD, Cox regression models were implemented. In addition to nonlagged models, lagged models incorporating a 10-year lag period were run as a sensitivity analysis to account for chronic disease mortality latency. Results from these analyses (data not shown) were similar to findings from the nonlagged models, described here.

As part of the regression analysis, HRs and 95% CIs were adjusted for sex and other potential confounding exposure variables (age at hire, employment duration, period of hire, and beryllium facility type) (Tables 4, 5). Elevated HRs associated with increasing age at hire were observed for mortality from all causes, all cancers, lung cancer, bladder cancer, and ONMRD (Table 4 and Table 5). These HRs were of similar magnitudes of effect but ranged from 1.067 (lung cancer) to 1.112 (bladder cancer).

TABLE 5. Hazard Ratios and 95% Confidence Intervals of Bladder Cancer, Kidney Cancer, or CNS According to Sex, Age at Hire, Employment Duration, Period of Hire, and Type of Beryllium Facility

	Hazard Ratio (95% CI)		
Factor	**Bladder Cancer**	**Kidney Cancer**	**CNS**
Sex (male vs female)	4.71 (1.48–14.96)	2.54 (0.91–7.06)	1.38 (0.58–3.25)
Age at hire (1-year increase)	1.112 (1.085–1.139)	1.032 (0.997–1.069)	1.016 (0.981–1.052)
Employment duration (1+ year vs <1 year)	1.45 (0.89–2.36)	1.04 (0.59–1.85)	1.39 (0.74–2.58)
Period of hire (1955 or later vs before 1955)	0.68 (0.41–1.14)	0.66 (0.35–1.24)	1.16 (0.61–2.18)
Type of beryllium plant (mixed vs insoluble)	1.09 (0.64–1.85)	0.57 (0.31–1.02)	0.90 (0.48–1.66)

CI, confidence interval; CNS, Cancer of Central Nervous System.

Elevated HRs were observed between employment duration of 1 year or more and mortality from ONMRD, bladder cancer, and CNS compared to employment of less than 1 year; however, this association was statistically significant only for ONMRD. Employees who were employed for at least 1 year had an elevated risk of mortality from ONMRD compared to those who had worked for less than 1 year (HR: 1.25, 95% CI: 1.01–1.56) (Table 4). Similar results were observed when employment duration was considered as a continuous variable in models (data not shown). There was an elevated HR for one additional year of employment for ONMRD (HR: 1.014, 95% CI: 1.005–1.022).

Generally, those who had been hired in 1955 and later had decreased HRs compared to those hired before 1955 (Tables 4, 5). Period of hire, categorized as 1955 or later or pre-1955, was associated with reduced mortality from all causes of death combined, all cancers, lung cancer, and ONMRD. These findings were supported by estimates from models where hire year was included as a continuous measure; there were decreased HRs with every additional year of hire for mortality from all causes (HR: 0.979, 95% CI: 0.977–0.981) and from all cancers (HR: 0.989, 95% CI: 0.985–0.992).

The association between type of beryllium facility and mortality from all causes was borderline statistically significant. After adjustment for other potential exposure confounders, the HR of all cause-mortality for mixed beryllium facility status was 1.05 (95% CI: 1.00–1.10, $P = 0.049$) compared to insoluble beryllium facility status (Table 4). Beryllium facility type was not found to be associated with risk of any other causes of death in survival analyses.

We also conducted a Cox regression sensitivity analysis of berylliosis cases ($n = 84$). While reduced mortality was observed between a later period of hire (1955 or later vs pre-1955) and ONMRD (HR: 0.61, 95% CI: 0.49–0.77), a nonsignificant association was seen for berylliosis (HR: 1.27, 95% CI: 0.77–2.09). The HR between employment duration and berylliosis remained statistically significantly elevated (HR: 3.89, 95% CI: 2.09–7.24). Additionally, while type of beryllium facility was not associated with ONMRD, a significantly elevated association was observed between mixed beryllium facility status and berylliosis, compared to insoluble beryllium facility status (HR: 1.89, 95% CI: 1.11–3.20).

Interactions between hire age and facility type, hire age and period of hire, and period of hire and facility type were identified in the regression model for mortality from all causes. These interaction terms were included in Cox models in addition to potential confounders (sex, hire age, duration of employment, period of hire, and beryllium facility type); select HRs and 95% CIs from these models are presented in Table 6. Models are not presented for mortality due to bladder cancer, kidney cancer, or CNS, due to model overfitting when the identified interaction terms were included because of the relatively low number of observed deaths. For mortality due to all cancers, the P values of the interaction terms of hire age and beryllium facility type, hire age and period of hire, and period of hire and beryllium facility type were 0.047, <0.0001, and <0.0001, respectively. The P values of the interaction terms between hire age and period of hire were 0.048 for lung cancer and 0.043 for ONMRD mortality.

Overall, HRs were elevated for a 1-year increase in age at hire when stratified by both period of hire and beryllium facility type. Considering the interaction between hire age and period of hire, the effect of hire age appeared to be similar or slightly elevated among those hired 1955 or later compared to those hired before 1955, except for all-cause mortality. Using lung cancer as an example, among employees in mixed facilities hired in 1955 or later, the HR of a 1-year increase in age at hire was 1.07 (95% CI: 1.06–1.09), while this HR among employees in mixed facilities hired before 1955 was 1.06 (95% CI: 1.04–1.07) (Table 6).

For the interaction between hire age and beryllium facility type, the effect of hire age either generally did not differ or was slightly decreased among those employed in insoluble beryllium facilities compared to those employed in mixed facilities. Using mortality due to all cancers as an example, among employees in mixed facilities hired before 1955, the HR or a 1-year increase in age at hire was 1.064 (95% CI: 1.057–1.071), while the HR among insoluble facility workers hired before 1955 was 1.08 (95% CI: 1.06–1.09) (Table 6).

For the interaction between period of hire and beryllium facility type, the effect of period of hire (1955 and later vs before 1955) was decreased overall and appeared to vary by type of beryllium facility (Table 6). The reduced HR associated with a hire period of 1955 or later compared to an earlier hire period, was often more pronounced among those employed at mixed beryllium facilities (e.g., lung cancer HR: 0.61, 95% CI: 0.50–0.73) compared to those employed at insoluble beryllium facilities (e.g., lung cancer HR: 0.80, 95% CI: 0.57–1.11) (Table 6). These reduced HRs associated with a later hire period were observed for all outcomes among mixed facility employees, and with all-cause and all cancer mortality among insoluble facility employees. Conversely, the effect of type of beryllium facility varied when stratified by period of hire. Among those hired before 1955,

TABLE 6. Hazard Ratios and 95% Confidence Intervals of Overall Mortality, All Cancers, Lung Cancer, or ONMRD According to Sex, Age at Hire, Employment Duration, Period of Hire, and Type of Beryllium Plant and Interactions*

	Hazard Ratio (95% CI)			
Factor	**All Cause of Death**	**All Cancer**	**Lung Cancer**	**ONMRD**
Sex (male vs female)	1.56 (1.46–1.67)	1.66 (1.45–1.90)	2.45 (1.85–3.23)	1.26 (0.93–1.70)
Age at hire (1-year increase) and *period of hire before 1955*, stratified by type of beryllium plant				
Insoluble	1.098 (1.092–1.103)	1.08 (1.06–1.09)	1.07 (1.05–1.09)	1.09 (1.06–1.12)
Mixed	1.093 (1.090–1.96)	1.064 (1.057–1.071)	1.06 (1.04–1.07)	1.08 (1.07–1.10)
Age at hire (1-year increase) and *period of hire 1955 or later*, stratified by type of beryllium plant				
Insoluble	1.087 (1.083–1.091)	1.08 (1.07–1.09)	1.09 (1.07–1.11)	1.12 (1.09–1.14)
Mixed	1.082 (1.078–1.086)	1.07 (1.06–1.08)	1.07 (1.06–1.09)	1.11 (1.09–1.13)
Employment duration (1+ year vs <1 year)	0.98 (0.93–1.02)	1.00 (0.92–1.09)	1.04 (0.89–1.21)	1.26 (1.01–1.57)
Period of hire (1955 or later vs before 1955) stratified by type of beryllium plant†				
Insoluble	0.77 (0.70–0.84)	0.76 (0.64–0.90)	0.80 (0.57–1.11)	0.65 (0.41–1.05)
Mixed	0.60 (0.56–0.63)	0.76 (0.68–0.85)	0.61 (0.50–0.73)	0.57 (0.44–0.75)
Type of beryllium plant (mixed vs insoluble) stratified by period of hire†				
Before 1955	1.23 (1.14–1.34)	0.98 (0.83–1.14)	1.31 (0.97–1.76)	1.33 (0.89–2.00)
1955 or later	0.95 (0.89–1.02)	0.98 (0.86–1.10)	1.00 (0.80–1.24)	1.17 (0.84–1.63)

CI, confidence interval; ONMRD, other nonmalignant respiratory disease.

*Interactions terms included in models are age at hire and type of facility, age at hire and period of hire, and period of hire and type of facility.

†Reference age of hire of 31.1 years.

working at a mixed beryllium facility was associated with an elevated HR compared to working at an insoluble beryllium facility for all-cause mortality (HR: 1.23, 95% CI: 1.14–1.34), ONMRD (HR: 1.33, 95% CI: 0.89–2.00), and lung cancer (HR: 1.31, 95% CI: 0.97–1.76) (Table 6). In comparison, among those hired in 1955 or later, employment at facilities with mixed beryllium exposure was associated with an effect closer to the null (all-cause mortality HR: 0.95, 95% CI: 0.89–1.02; ONMRD HR: 1.17, 95% CI: 0.84–1.63; lung cancer HR: 1.00, 95% CI: 0.80–1.24).

Tests for Trend

Results for tests for linear trend are presented in Supplemental Table 8 (http://links.lww.com/JOM/C11). No significant increasing trends were observed between mortality for lung cancer and duration of employment and time since hire. Significant increasing trends were observed between ONMRD and length of employment ($P < 0.001$) and time since hire ($P < 0.05$). Significant increasing linear trends ($P < 0.05$) were seen between various causes of death (including all cancers, kidney cancer, cancer of CNS, potential mesothelioma) and time since hire and duration of employment, as expected given the chronic etiology of the diseases, though generally the SMRs were nonsignificant.

DISCUSSION

The present analysis extends the years of follow-up and expands the largest cohort of beryllium workers studied to date. The majority of causes of death evaluated were not elevated compared to the US population. Among the total cohort, only mortality due to ONMRD was elevated.

Overall, results showed consistent elevations in mortality across analyses for ONMRD. In analyses, ONMRD was evaluated as a broader category that contained the specific ICD category, “berylliosis” (ICD-10 code J63.2), as defined in Supplemental Table 2 (http://links.lww.com/JOM/C5). Historically, berylliosis has been used interchangeably to refer to ABD and CBD.[1] This study was not intended to examine CBD separately from ONMRD. In fact, several factors prevented our ability to present a valid estimation of mortality risk for CBD. Additionally, the ICD categorization of berylliosis, which includes both ABD and CBD, makes no distinction between acute and chronic beryllium diseases (a factor contributing to our inability to examine ABD and CBD separately). However, it may be plausible to assume that most of berylliosis deaths observed ($n = 84$) were due to CBD, since all observed berylliosis deaths occurred after the mid-1950s and previous reports suggest that deaths from ABD did not occur after the late 1940s.[17,18] Still, the current study utilized the ONMRD mortality grouping due to concern that a portion of deaths due to beryllium disease could be misclassified as other ONMRD diseases, such as “lung diseases due to external agents” ($n = 55$), and “interstitial lung diseases” ($n = 47$). The ONMRD grouping includes berylliosis deaths that may have been misclassified as other diseases under this category. In a previous analysis of this cohort, upon review of available death certificates whose underlying cause of death was classified under ONMRD, an additional 2 certificates (12%), with nonberylliosis underlying causes, were identified as likely misclassified berylliosis-related deaths.[11] Assuming the reviewed certificates were a representative sample, up to 5 additional deaths may have been due to berylliosis, and 13% of all ONMRD deaths due to berylliosis may have been misclassified in the previous analysis.[11] Additionally, because of limitations of the mortality data published by the CDC WONDER online database (suppression of small data counts across demographic categories to avoid revealing the identities of individual people), we were unable to calculate appropriate reference rates and corresponding separate SMRs for berylliosis or CBD.

Conclusions made regarding CBD or berylliosis based on our findings presented on the broader ONMRD category are cautioned, given the potential diluting effect of the broader ONMRD grouping. However, in a sensitivity analysis we performed Cox regression modeling of observed berylliosis deaths, and observed that longer employment duration and employment at mixed beryllium facilities were associated with statistically significantly elevated risk of berylliosis, which supports patterns observed for ONMRD mortality.

As shown in Supplemental Table 2 (http://links.lww.com/JOM/C5), the ONMRD category also included 125 deaths from causes further categorized as “chronic airways obstruction not otherwise specified,” which likely obscured the potential association with CBD. Unfortunately, due to similar data limitations for reference rates as mentioned above, calculating SMRs excluding this group of deaths was not feasible. Studies by other authors that have examined mortality among similar samples of beryllium manufacturing workers have also been restricted in their analyses to examine groupings containing but unable to distinguish berylliosis and CBD (“Pneumoconiosis and other respiratory diseases,”[8] “Pneumoconiosis and other respiratory disease” and “Pneumoconiosis excluding asbestosis and silicosis”).[7] Finally, we considered possible misclassification of CBD and berylliosis with sarcoidosis, which is not included under ONMRD. Given similar clinical presentations, CBD has been reported to be misdiagnosed as sarcoidosis.[19] However, less than five deaths attributable to sarcoidosis were identified, suggesting that potential misclassification of CBD and berylliosis as sarcoidosis was not a significant issue in this cohort. Additionally, as the plants in this study all had CBD prevention programs with the early sites studied and/or actively monitored and evaluated by the Atomic Energy Commission beginning in the 1940s, it is unlikely that a CBD case would be misdiagnosed.

Results in this follow-up study align with the results previously reported by Boffetta et al (2016). In the general analysis, ONMRD was elevated for the total cohort and for both male and female workers. These elevations were present among workers in facilities with mixed beryllium exposure, but not in workers at facilities with insoluble beryllium exposure. Further analyses were conducted to evaluate characteristics contributing to the elevation. When analyzed by period of hire, statistically significant SMRs were observed among workers with mixed beryllium exposure hired prior to 1955. In the same group of workers, statistically significant SMRs were detected in analyses by facility, as well as a trend with increasing duration of employment. These results were confirmed in the Cox model analysis, without evidence of an interaction between employment duration and beryllium facility type.

Lung cancer mortality was elevated among all workers with exposure to mixed beryllium. Additional analyses of mixed beryllium facility workers also revealed elevated lung cancer mortality among those who had been hired prior to 1955 as well as short-term workers (defined as workers with less than 1 year of employment). This was consistent with a case-control study of employees at a single mixed beryllium manufacturing facility located in Reading, Pennsylvania conducted by Sanderson et al (2001), which reported lung cancer cases had a shorter length of employment. Sanderson et al (2001) reported the cumulative beryllium exposure of workers at the facility were lower when compared to controls but higher when evaluated by lag duration.[20] This finding is also consistent with research in other industries indicating a difference in mortality patterns between short-term and long-term workers.[21] Factors other than exposure that could not be evaluated in the present study could be contributing to increased mortality in short-term workers, such as prior or subsequent occupational exposures, higher smoking habits, and multiple chemical exposures (e.g., acid mists, free silica) while working at beryllium facilities.[22–24] Trend analysis showed a reduction in SMRs for lung cancer deaths among workers hired 1955 and later versus prior to 1955, while it did not show a trend in the total cohort for soluble/mixed facilities by length of employment. Statistically significant trends were seen for time since hire, a surrogate for cumulative exposures, as expected.

Significantly elevated mortality risks for select causes of death were only observed among facilities where both soluble and insoluble forms beryllium had been processed (mixed facilities). This included SMRs for lung cancer and ONMRD for the Lorain facility, which was operational prior to 1950, and the Reading facility prior to 1965. Significantly elevated SMRs for ONMRD were also observed for the Elmore (1952–2020) and Delta facilities (1968–2020). Only nonsignificant associations were observed for insoluble beryllium facilities. These findings support previous results that have reported variation in mortality by facility.[8] The 1992 study by Ward et al included seven facilities also included in the current study. Significant elevations were reported only for the Lorain (mixed facility) and Reading facilities (Ward et al (1992) did not differentiate between pre- and post-1965 operation) but not the Cleveland facility (insoluble facility). The lack of quantitative exposure data is a limitation of our current study. Type of facility was used as a surrogate for potential exposure to different beryllium forms and the use of the "mixed facility" category allows flexibility in the consideration of commonplace factors such as job transfers during employment and other unrecorded activities or interactions within mixed facilities. However, this may represent a source of exposure misclassification for those workers at mixed facilities who had no exposure to soluble forms of beryllium. Comparisons of our findings to studies that evaluate individual-level exposure data should be made or considered cautiously.

Our study findings of no elevated mortality among insoluble only facilities do not support findings from a previous study of two beryllium facilities (Elmore and Hazelton). In this two facility analysis, Schubauer-Berigan et al (2017) described the facilities as beginning operation in the 1950s, having low exposure levels compared to other facilities (mean 1.3 μg/m^3), and though soluble and insoluble forms of beryllium were processed within the facilities, as having predominantly insoluble exposures. This 2017 analysis reported that increasing exposures at these facilities were associated with monotonic increases in lung cancer mortality.[25] The study authors concluded that their findings supported findings from their overall pooled cohort analysis[7] that was used by the US Occupational Safety and Health Administration in a lung cancer risk assessment to establish exposure limits for employees in the modern beryllium industry (insoluble exposures). We have previously evaluated the findings of Schubauer-Berigan et al (2017) in detail elsewhere,[10] although the main points are discussed briefly here. First, though the exposures to the workers in 2017 analysis by Schubauer-Berigan et al are described as predominantly insoluble,[25] it would be incorrect to equate that to exposure to only insoluble beryllium. The 2017 analysis did not present stratified results (insoluble only, mixed, soluble only), although the data were available. In our current analysis, we were able to cleanly stratify results by known facility status (insoluble or mixed) as well as by facility (Table 2; Supplemental Table 6, http://links.lww.com/JOM/C9, and Supplemental Table 7, http://links.lww.com/JOM/C10) and all results show no elevated mortality among insoluble only facilities. This is further supported by our internal comparisons and sensitivity analyses. Second, soluble beryllium exposure cannot be assumed to be mitigated because of other predominant exposures (e.g., insoluble beryllium) when considering the effect of this exposure on the potential development of lung cancer. Additionally, the exposure-response coefficients reported in Schubauer-Berigan et al (2017) were unexpectedly higher in the analysis of two low exposure facilities than in the analysis of seven facilities with higher exposure, and this discrepancy was not addressed.[7,25] There was also a lack of clarity on how the exposure matrices and exposure estimates may have impacted the epidemiological analyses and absence of adjustment for confounders that should be considered in the calculation of HRs.

In the current study, the SMR for COPD among the total cohort was nonsignificant (SMR: 0.99; 95% CI: 0.89–1.10). However, significant elevations in mortality risk were observed in additional analyses by period of hire and beryllium facility type. Significant risk of COPD was evident among workers who were hired prior to 1955 with mixed beryllium exposures, driving a similar association seen among all workers hired prior to 1955. Significant risk of COPD was not evident for those employed at insoluble beryllium facilities during any time period. Additionally, no significant associations for COPD were observed among workers hired in 1955 or later, regardless of type of beryllium exposure. These findings could further explain results from previous reports of elevated mortality due to COPD for workers exposed to beryllium.[7]

Based on 14 observed deaths, a significantly elevated SMR for tuberculosis was also observed among workers with mixed beryllium exposures who had been hired prior to 1955. As an infectious respiratory disease, occupational exposure is not likely to be a significant contributing factor to the disease's etiology. The inability to access area-specific reference data for the time periods of interest (state-level, county-level, etc) prevented further comparisons that may have been able to consider the effect of potentially confounding factors on the observed elevations. Another factor that could have contributed to this observed elevation could be concomitant tuberculosis and silicosis (one of the causes of death included in the ONMRD grouping), as silicosis and exposure to free silica have been reported to be associated with increased tuberculosis risk.[26] The current analysis did not include information on other potential chemical exposures, including free silica.

The potential for a "healthy worker effect" (HWE) was considered as a HWE could obscure risks associated with occupational exposures if workers of poorer health left the workforce at a disproportionate rate, contributing to an overall health advantage compared to the comparison population. This possibility has been raised in previous studies in this population.[7,17,27] As previously reported by Boffetta et al (2016), the HWE in this cohort might contribute to an underestimation of the mortality risk of lung cancer and ONMRD when the worker cohort is compared with external (nonworker) populations.[9] For the present SMR analysis, there does appear to be a HWE which is evident when causes of death most likely unrelated to workplace exposures are considered. Significantly reduced SMRs are present for causes of death such as heart disease and diabetes, not only among the total cohort but also subgroups with assumed reduced exposures (workers of insoluble facilities only, or workers hired in 1955 or later). Therefore, it should be considered that SMRs for *a priori* causes of death that were close to the null value might have been attenuated due to HWE. We performed internal comparisons by way of Cox model analyses to adjust for covariates and time-varying factors, to compare to trends and patterns observed in the SMR analyses. Overall, the results of the Cox model analyses supported the general trends of the main SMR analyses reported for *a priori* causes of death: elevated mortality among workers of mixed facilities compared to insoluble facilities and reduced mortality among those hired after 1955 compared to those hired prior to 1955. This is in line with previous suggestions that the HWE would not fully explain trends in results reported based on internal comparisons,[9] such as those in Tables 4–6.

The study had multiple strengths, including the long duration of follow-up as well as the large sample size and minimal loss to follow-up. However, the shorter duration of employment for many workers (<1 year), as well as the lack of information on tobacco use, exposures to other chemicals (e.g., silica, acid mist), occupations outside the beryllium industry, job title, and quantitative exposure information are limitations. The present study considered these limitations through robust sensitivity analyses and examination of exposure surrogates, which generally supported results from the main analyses.

State mortality rates which can adjust for shared environmental and beryllium industry employment factors were not used for comparison for the present analysis due to the inability to report low sample size counts. Thus, factors including tobacco smoking, employment in other high-risk industries, and other factors could not be considered in statistical analyses. Elevations seen when compared to the US population in causes of death such as tuberculosis, for example, may be attenuated or null compared to State mortality rates due to a strong geographic heterogeneity. While this could not be evaluated in the current study, previous analyses within this cohort did not demonstrate extensive differences.[9]

To address several of the limitations that have presented in evaluating this cohort, a current research effort is underway to conduct a detailed assessment of exposure to beryllium by constructing a comprehensive job exposure matrix (JEM) and conducting a nested case-control study, controlling for confounding factors. The objectives will be to evaluate the outcomes of the current analysis following exposure to different beryllium species (i.e., soluble vs insoluble); analyze the dose-response relationship between exposure to different beryllium species for these target causes of death; and to control for potential of confounding by body mass index, tobacco smoking, and other occupational exposures, and to assess the potential mediating effect of these factors on the associations with beryllium exposure.

This study provides further evidence supporting our 2016 study finding of no risk of lung cancer mortality among workers employed in facilities with insoluble-only beryllium exposure over any time period.[9] In addition, the study observed no elevated risk of lung cancer mortality for workers hired 1955 and later, regardless of mixed or insoluble beryllium exposures. Elevated risk of ONMRD, an ICD grouping containing deaths attributed to berylliosis, was observed only among workers hired prior to 1955 and those who had been employed in facilities that processed both soluble and insoluble beryllium. We also did not find evidence of increased risk of mortality due to all cancers, kidney cancer, bladder cancer, or cancer of CNS in this cohort, regardless of type of beryllium exposure. In light of this additional evidence, hazard classifications for insoluble forms of beryllium and soluble forms of beryllium should be separated to provide workers with the most evidence-based beryllium hazard communications. This could have a significant impact as insoluble forms of beryllium comprise over 99.9% of the beryllium used in commerce.

ACKNOWLEDGMENTS

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