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A Mortality Study of Workers at Seven Beryllium Processing Plants

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The International Agency for Research on Cancer (IARC) has found that the evidence for the carcinogenicity of beryllium is sufficient based on animal data but "limited" based on human data. This analysis reports on a retrospective cohort mortality study among 9,225 male workers employed at seven beryllium processing facilities for at least 2 days between January 1, 1940, and December 31, 1969. Vital status was ascertained through December 31, 1988. The standardized mortality ratio (SMR) for lung cancer in the total cohort was 1.26 (95% confidence interval [CI] = 1.12–1.42); significant SMRs for lung cancer were observed for two of the oldest plants located in Lorain, Ohio (SMR = 1.69; 95% CI = 1.28–2.19) and Reading, Pennsylvania (SMR = 1.24; 95% CI = 1.03–1.48). For the overall cohort, significantly elevated SMRs were found for "all deaths" (SMR = 1.05; 95% CI = 1.01–1.08), "ischemic heart disease" (SMR = 1.08; 95% CI = 1.01–1.14), "pneumoconiosis and other respiratory diseases" (SMR = 1.48; 95% CI = 1.21–1.80), and "chronic and unspecified nephritis, renal failure, and other renal sclerosis" (SMR = 1.49; 95% CI = 1.00–2.12). Lung cancer SMRs did not increase with longer duration of employment, but did increase with longer latency (time since first exposure). Lung cancer was particularly elevated (SMR = 3.33; 95% CI = 1.66–5.95) among workers at the Lorain plant with a history of (primarily) acute beryllium disease, which is associated with very high beryllium exposure. The lung cancer excess was not restricted to plants operating in the 1940s, when beryllium exposures were known to be extraordinarily high. Elevated lung cancer SMRs were also observed for four of the five plants operating in the 1950s for workers hired during that decade. Neither smoking nor geographic location fully explains the increased lung cancer risk. Occupational exposure to beryllium compounds is the most plausible explanation for the increased risk of lung cancer observed in this study. Continued mortality follow-up of this cohort will provide a more definitive assessment of lung cancer risk at the newer plants and among cohort members hired in the 1950s or later at the older plants. Further clarification of the potential for specific beryllium compounds to induce lung cancer in humans, and the possible contribution of other exposures in specific processes at these plants, would require a nested case-control study. We are currently assessing whether available industrial hygiene data would support such an analysis.

Key words: lung cancer, beryllium disease, occupational exposure, pneumoconiosis

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INTRODUCTION

The first cases of chemical pneumonitis in U.S. beryllium workers were reported in 1943 by Van Ordstrand et al. In 1949, the U.S. Atomic Energy Commission (AEC), then the prime consumer of beryllium, adopted an exposure standard of 2 $\mu g/m^3$ as a time-weighted average [Preuss, 1988]. In 1952, the Beryllium Case Registry (BCR) was established to collect data on the epidemiology and clinical features of beryllium-related diseases [Hardy et al., 1967; Sprince and Kazemi, 1980]. By that time, both acute and chronic forms of beryllium disease had been recognized [Hardy and Tabershaw, 1946].

The induction of lung cancer in rats by inhalation exposure to beryllium sulfate ($BeSO_4$) was first demonstrated in the 1950s [Groth, 1980]. The International Agency for Research on Cancer (IARC) evaluated the carcinogenicity of beryllium and beryllium compounds in 1980 and concluded that beryllium compounds are carcinogenic in three animal species (rats, rabbits, and monkeys) [IARC, 1980]. The IARC also concluded that lung tumors had been produced in rats by inhalation or intratracheal exposure to beryllium metal, beryllium-aluminum alloy, beryl ore, beryllium chloride, beryllium fluoride, beryllium hydroxide, and beryllium sulfate (or its tetrahydrate) and in monkeys, by inhalation or intratracheal exposure to beryllium oxide and beryllium sulfate.

Epidemiologic studies have been conducted of the mortality experience of individuals in the BCR [Infante et al., 1980; Steenland and Ward, 1991] and of two beryllium production cohorts [Mancuso and El-Attar, 1969; Mancuso, 1970, 1980; Wagoner et al., 1980]. The first BCR study, with follow-up through 1975, found a significantly increased risk of lung cancer among individuals with acute, but not chronic, beryllium disease (standardized mortality ratio [SMR] = 3.14) [Infante et al., 1980]. A recent study of the mortality of workers enrolled in the BCR at the National Institute for Occupational Safety and Health (NIOSH), with follow-up through 1988, found an excess risk of lung cancer (SMR = 2.00; 95% confidence interval [CI] = 1.33–2.89) which was most pronounced among individuals with acute disease (SMR = 2.32; 95% CI = 1.35–3.72) [Steenland and Ward, 1991]. The studies of beryllium production cohorts found significant excess risks of lung cancer with SMRs ranging from 1.37 [Wagoner et al., 1980] to 1.97 [Mancuso, 1980]. However, the results of these epidemiologic studies are not considered conclusive by some review bodies [IARC, 1980; Environmental Protection Agency, 1987], while others conclude that despite some limitations, the weight of the evidence supports the conclusion that beryllium is carcinogenic in humans [Workshop on Epidemiology, 1981; Saracci, 1985].

To examine further the mortality experience of workers exposed to beryllium, NIOSH conducted a retrospective cohort mortality study of seven beryllium production facilities in the United States. The cohort includes individuals employed by two companies in plants located in Reading and Hazelton, Pennsylvania, and Lorain, Cleveland (Perkins and St. Clair plants), Lucky, and Elmore, Ohio. The Reading and Lorain facilities were studied previously by Wagoner et al. [1980], Mancuso and El-Attar [1969], and Mancuso [1970,1980]. The analyses presented in this paper were conducted in 1991, and no interim publications have addressed this issue.

TABLE I. Years During Which Major Processes Were Conducted at the Beryllium Plants Included in the Study*

Plant location	Ore refining	Beryllium oxide production	Production of metal	Production of beryllium copper alloy	Machining
1. Lorain	1935–1948	1935–1948	1935–1948	1935–1947	—
2. Reading	1935–1966	1935–1966	—	1935–present	1938–present
3. Lucky	1950–1958	1950–1958	1950–1958	—	—
4. Perkins (Cleveland)	1937–1955	1937–1962	1948–1962	—	1941–1963
5. St. Clair (Cleveland)	—	—	—	—	1963–1973
6. Elmore	1958–1977	1958–present	1958–present	1952–present	1958–present
7. Hazelton	1958–1978	1958–1978	1958–1978	1958–1978	1958–1978

*The dates given are provided for the purpose of describing the processes only and were not used to restrict the cohorts. For example, workers hired at the Lucky plant in 1949 were included in the study, as were a few individuals hired to work at the Lorain plant in 1949 and early 1950.

BACKGROUND

The plants under study have been involved in various phases of beryllium processing, including the extraction of beryllium hydroxide from beryl ore, and production of beryllium oxide (beryllia), pure beryllium metal, and beryllium copper alloy, and machining of beryllium-containing products. The years of operation and major processes conducted at each plant are listed in Table I.

The primary source of beryllium during the time period of the study was beryl ore (beryllium aluminum silicate) which contains 10–12% beryllium oxide. Six of the seven plants in the study have been involved in ore extraction, which utilizes either a sulfate or fluoride process to produce beryllium hydroxide [Rice, 1988]. Potential exposures during ore processing operations include ore dust, silicon dioxide fumes, and acid mists and fumes ($BeSO_4$) [Laskin et al., 1950]. Six of the study plants produced beryllium oxide. Beryllium oxide (beryllia) is produced by calcining beryllium hydroxide, pressing the powder into desired shapes, and sintering the greenware in ceramic kilns [Preuss, 1988]. Potential exposures in this process include fumes of lead sulfide, copper sulfide, and sulphur trioxide, and dusts of beryllium oxide [Laskin et al., 1950]. Five of the study plants produced beryllium metal. This process involves heating beryllium hydroxide and ammonium fluoride and reducing the resulting beryllium fluoride with magnesium to metallic beryllium [Preuss, 1988]. Potential exposures include acid fluoride mists, fumes and dusts of beryllium ammonium fluoride, beryllium fluoride, hydrogen fluoride, ammonium fluoride, beryllium metal, and beryllium oxide [Laskin et al., 1950]. Four of the study plants produced beryllium copper alloy. Beryllium copper master alloy is produced in arc furnaces by adding beryllium hydroxide and carbon to copper [Preuss, 1988]. Potential exposures include beryllium oxide, copper, and beryllium copper alloy dusts and fumes [Laskin et al., 1950]. Five of the study plants also had machining operations. Machining involves potential exposure to respirable particles of beryllium and alloys, if not adequately controlled [Preuss, 1988].

Both industrial hygiene data and trends in the incidence of beryllium disease suggest that the greatest beryllium exposure occurred in the 1940s, prior to institution of controls mandated by AEC contracts in 1949–1951 [Eisenbud and Lisson, 1983].

It is estimated that air concentrations of beryllium in the 1940s frequently exceeded 1,000 $\mu g/m^3$ in the Lorain and Reading facilities [Eisenbud and Lisson, 1983], as compared to today's standard of 2 $\mu g/m^3$ [Occupational Safety and Health Administration (OSHA), 1989].

METHODS

The study population included all males who worked at least 2 days between January 1, 1940, and December 31, 1969. The 2-day minimum was selected to exclude individuals who were paid for undergoing their pre-employment examinations but never worked. A total of 9,225 males meeting the cohort entry criterion was identified. The work history information was limited to plant and to beginning and ending dates of employment. Missing race, sex, and date of birth information was obtained through the Social Security Administration (SSA).

Personnel records were matched against records of individuals identified from SSA form 941 quarterly earnings reports (QER) which were obtained from the study plants for all quarters from 1940 through 1967. QERs list all the employees of a company for every quarter in which they paid into the Social Security system. Lists of individuals who appeared on the QERs but not in the personnel files were sent to the companies for review. If no personnel information was available, individuals were considered eligible for the study only if they appeared on at least two QERs (because the cohort entry criterion of having worked at least 2 days could not be evaluated for persons appearing for only one quarter). Individuals who had worked for both companies or at multiple plants within the same company were combined into a "multiple plant" category in plant-specific analyses. In addition, data from the Perkins and St. Clair plants were combined, because their records were stored at the same site and the plant at which an individual worked was difficult to determine.

The vital status of all workers in the study was determined as of December 31, 1988. Sources used to determine vital status were the SSA, the Internal Revenue Service, post office cards mailed to the last known address, the Veteran's Administration, the Health Care Financing Administration, and the National Death Index. Death certificates were obtained from state vital statistics offices and were coded according to the ICD revision in effect at the time of death. The mortality experience of the cohort was analyzed using a modified life-table system (LTAS) developed by NIOSH [Steenland et al., 1990]. Life-table analyses were conducted for the total cohort and for each plant. In addition to life-table analyses using external referent rates, internal analyses were conducted using Poisson regression [Frome and Checkoway, 1985].

The influence of geographic variation in lung cancer mortality was evaluated by using county lung cancer rates in place of U.S. rates to generate the expected number of lung cancers. This analysis was restricted to 1950–1988 because county-specific rates for the 1940s were not available. For the plants located in Lucky and Elmore, Ohio, and Hazelton, Pennsylvania, the rates for several adjacent counties were combined to best represent the areas in which plant workers resided.

The potential effect of differences in smoking habits between the study cohort and the U.S. population on expected lung cancer mortality was evaluated using an adjustment procedure described by Axelson and Steenland [1988]. Information on smoking habits of the study population was obtained from a 1968 medical survey

conducted by the Public Health Service at the Reading, Hazelton, Elmore, and St. Clair (Cleveland) plants. This survey included 1,466 (15.9%) of the 9,225 cohort members. Information on smoking habits of the U.S. population was obtained from smoking surveys conducted in 1965 [National Cancer for Health Statistics (NCHS), 1981] and 1970 [Office of Health Research, Statistics, and Technology (OHRST), 1979]. The proportions of never, former, light (less than or equal to one pack), and heavy (more than one pack) smokers in the U.S. population were adjusted to the age distribution of the cohort. The lung cancer risks associated with each of these cigarette smoking categories were estimated to be 1 for never smokers, 6.5 for smokers of one pack or less, 13.8 for smokers of more than one pack, and 6.2 for former smokers [Hammond, 1966]. The estimated rate ratio (RR) for lung cancer of the cohort vs. the U.S. population, due to smoking differences alone, was calculated via the following equations [Axelson and Steenland, 1988]:

$$I_{exp} = 1(\%\text{nonsmoke})I_o + RR_{light}(\%\text{light})I_o + RR_{heavy}(\%\text{heavy})I_o + RR_{former}(\%\text{former})I_o$$

$$I_{nonexp} = 1(\%\text{nonsmoke})I_o + RR_{light}(\%\text{light})I_o + RR_{heavy}(\%\text{heavy})I_o + RR_{former}(\%\text{former})I_o,$$

where I_o is the rate for nonsmokers, I_{exp} is the rate among the cohort, and I_{nonexp} is the rate in the U.S. population. The proportions of never smokers, current heavy, current light, and former smokers in the exposed cohort and the U.S. population, and the known relative risks for each smoking category, were substituted in the above equations. Each equation was then solved for I_o, and then the two equations were set equal to each other ($I_o = kI_{exp} = k'I_{nonexp}$). The ratio I_{exp}/I_{nonexp} was then derived. The ratio I_{exp}/I_{nonexp} represents the RR between the exposed cohort and the nonexposed referent group due to the differences in smoking habits alone, without any consideration of possible occupational risks. I_{exp}/I_{nonexp} was calculated twice, using the 1965 and 1970 U.S. smoking prevalence rates, and then averaged to obtain the smoking adjustment factor (since smoking data from the cohort came from 1968). The expected number of lung cancers calculated in the life table were multiplied by the smoking adjustment factor to estimate the expected number of lung cancers after considering the cohort's smoking habits.

NIOSH maintains a BCR, which has recently been used to examine the mortality experience of workers with beryllium disease [Steenland and Ward, 1991]. Records of individuals in the current study were matched against records in the NIOSH BCR mortality study [Steenland and Ward, 1991] to estimate the proportion of workers at each plant who had beryllium disease, and to identify workers with beryllium disease at the Lorain plant so that their mortality experience could be analyzed separately. To avoid the possible bias that workers who died of lung cancer were more likely to be reported to the registry, workers were excluded from the BCR mortality study file if they were reported to the registry after death.

Based on previous studies, the a priori outcomes of interest in this study included lung cancer, nonmalignant respiratory disease (excluding influenza and pneumonia), and heart disease. Within the major category of nonmalignant respiratory disease, deaths from "berylliosis" are included in the category "pneumoconiosis and other respiratory diseases." Within the cardiovascular diseases, deaths related to cor

TABLE II. Vital Status as of Study End Date (12/31/88) Among U.S. Male Beryllium Workers Employed 1940–1969

Plant location	Alive (%)	Deceased (%)	Unknown (%)	Total
1. Lorain	504 (42.3)	596 (50.0)	92 (7.7)	1,192
2. Reading	1,852 (51.9)	1,602 (44.9)	115 (3.2)	3,569
3. Lucky	267 (65.9)	126 (31.1)	12 (3.0)	405
4. Cleveland[a]	1,080 (67.8)	473 (29.7)	40 (2.5)	1,593
5. Elmore	1,132 (85.6)	178 (13.4)	13 (1.0)	1,323
6. Hazelton	498 (83.1)	95 (16.1)	5 (0.8)	590
Multiple plants	159 (61.9)	91 (35.4)	7 (2.7)	257
Unknown (QERs)[b]	197 (66.5)	79 (26.7)	20 (6.8)	296
Total	5,681 (61.6)	3,240 (35.1)	304 (3.3)	9,225

[a]St. Clair and Perkins plants combined.
[b]This category represents 295 individuals identified from SSA Quarterly Earnings Reports, for whom no personnel record could be located, and one individual for whom a specific plant location could not be determined from the personnel record.

pulmonale, a recognized complication of beryllium disease, are included in the category "Diseases of the arteries, veins, and pulmonary circulation." We present 95% CIs and two-sided p-values throughout the paper. CIs and p-values were calculated using Fisher's Exact method (if either the observed or expected was less than 10) or an approximate method (if observed and expected frequencies were 10 or more) [Rothman and Boice, 1979].

RESULTS

The study cohort included 8,905 white and 320 nonwhite males. Table II shows the vital status of workers by plant location. The "multiple plant" category in Table II represents 15 individuals who worked for both companies and 242 who worked at multiple plants within the same company. The "Unknown/(QER)" category represents 295 individuals identified from QERs and one for whom a specific plant location could not be determined from the personnel record. In the total cohort 5,681 (61.6%) persons were alive, 3,240 (35.1%) were deceased, and 304 (3.3%) had unknown vital status. Death certificates were obtained for 3,194 (98.6%) of the individuals known to be deceased. Vital status ascertainment was lowest for the Lorain plant, which ceased operation in 1948, and for individuals in the "Unknown/(QER)" category. The proportion of the cohort found to be deceased ranged from 13.4% at the Elmore plant to 50.0% at the Lorain plant.

Table III shows the numbers of workers by duration of employment and plant location. The cohorts identified from the six plant locations differ considerably in latency and duration of exposure characteristics. Certain plants in the study had very high employee turnover (84.6% of workers at the Lorain plant were employed less than 1 year) while others had a highly stable workforce. Table IV shows the distribution of person-years-at-risk (PYAR) by latency and plant location. The two oldest plants, Lorain and Reading, contribute 58.0% of the PYAR in the category of 15 or more years of latency. By contrast, the two newest plants, Elmore and Hazelton, together contribute only 14.4% of the PYAR in the 15 or more years latency category. Because the study plants differ with respect to latency and duration of employment,

TABLE III. Numbers of Persons by Duration of Employment and Plant Location Among U.S. Male Beryllium Workers Employed 1940–1969

	Duration of employment (years)				
	<1	1–5	5–10	>10	
Plant location	Number (%)	Number (%)	Number (%)	Number (%)	Total
1. Lorain	1,008 (84.6)	153 (12.8)	30 (2.5)	1 (0.1)	1,192
2. Reading	1,921 (53.8)	795 (22.3)	238 (6.7)	615 (17.2)	3,569
3. Lucky	252 (62.2)	145 (35.8)	7 (1.7)	1 (0.2)	405
4. Cleveland[a]	753 (47.3)	475 (29.8)	132 (8.3)	233 (14.6)	1,593
5. Elmore	385 (29.0)	329 (24.9)	150 (11.3)	459 (34.7)	1,323
6. Hazelton	116 (19.7)	105 (17.8)	108 (18.3)	261 (44.2)	590
Multiple plants (including both companies)	2 (0.8)	31 (12.1)	44 (17.1)	180 (70.0)	257
Unknown (QERs)	146 (49.3)	123 (41.6)	18 (6.1)	9 (3.0)	296
Total	4,583 (49.7)	2,156 (23.4)	727 (7.9)	1,759 (19.1)	9,225

[a]St. Clair and Perkins combined.

TABLE IV. Person-Years-at-Risk by Latency and Plant Location Among U.S. Male Beryllium Workers Employed 1940–1969

	Latency (years)		
Plant location	<15	>15	Total
1. Lorain	15,766	22,592	38,358
2. Reading	49,525	58,461	107,986
3. Lucky	5,690	7,543	13,233
4. Cleveland[a]	22,743	22,555	45,298
5. Elmore	19,206	14,011	33,217
6. Hazelton	8,630	6,208	14,838
Multiple plants (including both companies)	3,784	4,932	8,716
Unknown (QERs)	4,057	3,532	7,589
Total	129,401	139,834	269,235

[a]St. Clair and Perkins combined.

as well as processes and extent of beryllium exposure, we report mortality data for individual plants as well as for the overall cohort.

Table V summarizes the mortality experience of the entire cohort. Causes of death were selected for presentation if they were of a priori interest or there was a statistically significant excess in a major or minor category of death (two-sided p-value < 0.05). Appendix provides a more complete listing of SMRs by cause of death. An excess was observed in mortality from all causes (SMR = 1.05; CI = 1.01–1.08), which is largely accounted for by excess deaths from lung cancer and nonmalignant respiratory disease. A significantly elevated SMR was noted for "ischemic heart disease" (SMR = 1.08; CI = 1.01–1.14) but not for "diseases of the arteries, veins, and pulmonary circulation" (SMR = 1.13; CI = 0.91–1.39). Within the major category of nonmalignant respiratory disease, there was a significant elevation in mortality from "pneumoconiosis and other respiratory diseases" (SMR = 1.48; CI = 1.21–1.80). Among causes of death that were not specified a priori, there was a significant excess of deaths from "chronic and unspecified ne-

TABLE V. SMRs for Selected Major and Minor Causes of Death Among U.S. Male Beryllium Workers Employed 1940–1969 and Followed Through 12/31/88—Overall Cohort

Cause of death	Obs	Exp	SMR	95% CI
Malignant neoplasm of respiratory system	289	233.8	1.24[a]	1.10–1.39
Malignant neoplasm of trachea, bronchus, and lung	280	221.5	1.26[a]	1.12–1.42
Diseases of the heart	1,314	1,240.1	1.06[b]	1.00–1.12
Ischemic heart disease	1,094	1,017.5	1.08[b]	1.01–1.14
Other diseases of the circulatory system	281	283.7	0.99	0.88–1.11
Diseases of the arteries, veins and pulmonary circulation	90	79.8	1.13	0.91–1.39
Diseases of the respiratory system	229	189.4	1.21[a]	1.06–1.38
Emphysema	46	34.3	1.34	0.98–1.79
Pneumoconiosis and other respiratory diseases	101	68.2	1.48[a]	1.21–1.80
Diseases of the genitourinary system	51	44.3	1.15	0.86–1.51
Chronic and unspecified nephritis, renal failure, and other renal sclerosis	30	20.2	1.49[b]	1.00–2.12
All cancers	703	661.5	1.06	0.99–1.14
All deaths	3,240	3,091.6	1.05[a]	1.01–1.08

[a]Two-sided p-value less than 0.01.
[b]Two-sided p-value less than 0.05.

phritis, renal failure, and other renal sclerosis" (SMR = 1.49; CI = 1.00–2.12). The SMR for this category of renal disease was significantly elevated at the Lorain plant (SMR = 2.32; CI = 1.00–4.59).

When the a priori causes of death are examined by individual plant, it is apparent that significant excesses in lung cancer, cardiovascular disease, and non-malignant respiratory disease are confined to two of the oldest plants (Table VI). Both the Lorain and Reading plants have significant excesses of lung cancer (SMR = 1.69 and 1.24, respectively). Only the Reading plant has a significant increase in deaths from "ischemic heart disease" (SMR = 1.12), and only the Lorain plant has a significant increase in deaths from "diseases of the arteries, veins, and pulmonary circulation" (SMR = 1.78). The SMR for "pneumoconiosis and other respiratory diseases" is significantly elevated at the Lorain plant (SMR = 1.94), but not at the Reading plant (SMR = 1.34).

Among the four plants which were not previously studied, the SMRs for lung cancer range from 0.82 (Lucky) to 1.39 (Hazelton), and were not statistically significant. There were no significant excesses detected in other causes of death. The elevated lung cancer SMR for Hazelton was paralleled by an elevated SMR of 2.00 for "pneumoconiosis and other respiratory diseases." Individuals who worked in multiple plants had an SMR for lung cancer of 1.67 and for "pneumoconiosis and other respiratory diseases" of 2.60, consistent with the SMRs at the Lorain plant where many of these individuals were employed for part of their work history. Individuals in the "Unknown (QER)" category had a significant excess of "pneumoconiosis and other respiratory diseases" based on eight cases.

Table VII shows the risk of lung cancer by latency and duration of employment in the overall cohort. The SMRs for lung cancer tended to increase with increasing latency, and were statistically significant in the latency interval of 30 or more years. In contrast, there was no apparent trend of increasing risk with increasing duration of employment. Lung cancer was consistently elevated in all duration of employment categories, but was only significant in the less than 1 year category where there was

TABLE VI. SMRs for Selected Causes of Death by Plant Location Among U.S. Male Beryllium Workers Employed 1940–1969 and Followed Through 12/31/88

	Malignant neoplasm of trachea, bronchus, lung		Ischemic heart disease		Diseases of the arteries, veins, and pulmonary circulation		Pneumoconiosis and other respiratory diseases		All deaths	
Plant location	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
1. Lorain	57	1.69[a]	172	1.05	23	1.78[b]	20	1.94[a]	596	1.21[a]
2. Reading	120	1.24[b]	552	1.12[a]	47	1.19	41	1.34	1,602	1.09[a]
3. Lucky	9	0.82	45	0.98	3	0.87	3	0.87	126	0.91
4. Cleveland[c]	44	1.08	178	1.08	8	0.63	15	1.22	473	0.93
5. Elmore	15	0.99	59	1.06	2	0.48	3	0.69	178	0.91
6. Hazelton	13	1.39	30	0.93	4	1.76	5	2.00	95	0.89
Multiple plants	13	1.67	32	0.98	2	0.84	6	2.60	91	0.94
Unknown (QERs)	9	1.33	26	0.88	1	0.42	8	3.47[a]	79	0.88
Total	280	1.26[a]	1094	1.08[b]	90	1.13	101	1.48[a]	3,240	1.05[a]

[a]Two-sided p-value less than 0.01.
[b]Two-sided p-value less than 0.05.
[c]St. Clair and Perkins combined.

TABLE VII. SMRs for Lung Cancer in the Total Cohort by Latency and Duration of Employment Among U.S. Male Beryllium Workers Employed 1940–1969 and Followed Through 12/31/88

	Duration of employment (years)									
Latency	<1		1–5		5–10		>10		Total	
(years)	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
<10	5	0.78	3	0.61	2	0.71	—	—	10	0.70
10–15	9	1.32	4	0.94	2	1.38	2	0.55	17	1.05
15–20	14	1.30	9	1.39	2	0.95	7	1.17	32	1.26
20–25	10	0.66	12	1.40	3	1.20	11	1.39	36	1.06
25–30	28	1.48[a]	10	1.10	3	1.09	10	1.12	51	1.29
>30	86	1.52[b]	23	1.29	9	1.77	16	1.30	134	1.46[b]
Total	152	1.32[b]	61	1.19	21	1.26	46	1.19	280	1.26[b]

[a]Two-sided p-value less than 0.05.
[b]Two-sided p-value less than 0.01.

the largest number of observed deaths. Table VIII presents lung cancer SMRs, by plant, for three latency categories (<15 years, 15–30 years, and >30 years), and Tables IX and X present lung cancer SMRs by three latency categories (<15 years, 15 to 30 years, and >30 years) and four duration of employment categories (<1 year, 1–5 years, and 5–10 years, and >10 years) for the Lorain and Reading plants. Although limited by small numbers, the Lorain data suggest that the highest lung cancer risk occurred among workers with 1–5 years duration of employment, and that risk peaked in the 15–30 years latency category. At Reading, the highest lung cancer SMRs were observed among workers with <1 year duration of employment and the risk was highest in the >30 years of latency category.

Mortality from lung cancer was also examined by decade of hire. There ap-

TABLE VIII. Beryllium Workers' Lung Cancer Deaths by Plant Worked and Latency Among U.S. Male Beryllium Workers Employed 1940–1969 and Followed Through 12/31/88*

	Latency <15 years			Latency 15–30 years			Latency >30 years			Total		
Plant	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
1. Lorain	1	2.6	0.38	21	10.0	2.09[a]	35	21.1	1.66[b]	57	33.8	1.69[a]
2. Reading	9	11.5	0.78	44	37.5	1.17	67	47.9	1.40[b]	120	96.9	1.24[b]
3. Lucky	1	1.0	0.96	4	4.7	0.85	4	5.3	0.76	9	11.0	0.82
4. Cleveland[c]	9	6.9	1.30	20	22.0	0.91	15	11.8	1.27	44	40.7	1.08
5. Elmore	2	3.9	0.51	12	10.5	1.14	1	0.8	1.31	15	15.2	0.99
6. Hazelton	4	2.1	1.91	9	7.1	1.26	0	0.2	—	13	9.4	1.39
Multiple plants	0	0.7	—	4	3.2	1.23	9	3.8	2.38[b]	13	7.6	1.67
Unknown/QERs	1	1.6	0.64	5	3.9	1.28	3	1.3	2.30	9	6.8	1.33
Total	27	30.3	0.89	119	99.1	1.20[b]	134	92.1	1.46[a]	280	221.5	1.26[a]

*QER; quarterly earning report.
[a]Two-sided p-value less than 0.01.
[b]Two-sided p-value less than 0.05.
[c]St. Clair and Perkins combined.

TABLE IX. SMRs for Lung Cancer at the Lorain Plant by Latency and Duration of Employment in Study of U.S. Male Beryllium Workers Employed 1940–1948 and Followed Through 12/31/88

	Duration of employment (years)									
	<1		1–5		5–10		>10		Total	
Latency (years)	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
<15	1	0.48	0	—	0	—	0	—	1	0.38
15–30	16	1.89	4	3.14	1	3.31	0	—	21	2.09[b]
>30	29	1.68[a]	6	2.02	0	—	0	—	35	1.66[a]
Total	46	1.65[b]	10	2.12[a]	1	0.83	0	—	57	1.69[b]

[a]Two-sided p-value less than 0.05.
[b]Two-sided p-value less than 0.01.

peared to be a relationship between earlier decade of hire and increased lung cancer risk: prior to 1950 Obs = 1.77, SMR = 1.42 (CI = 1.25–1.62); 1950s Obs = 85, SMR = 1.24 (CI = 1.03–1.49); 1960s Obs = 18, SMR = 0.62 (CI = 0.40–0.92). This high SMR among workers hired prior to 1950 was heavily influenced by the Lorain plant, which had a lung cancer SMR of 1.69 (1.28–2.19) and closed in 1948 (see Table IX). Plant-specific analyses (Table XI) showed that two of the three plants operating in the 1940s had elevated lung cancer SMRs among workers hired during that decade: Reading SMR = 1.26; CI = 1.02–1.56; Lorain SMR = 1.69; CI = 1.28–2.19. Four of the five plants operating in the 1950s had elevated lung cancer SMRs among workers hired during that decade: Reading SMR = 1.42; CI = 0.93–2.08; Cleveland SMR = 1.32; CI = 0.86–1.93; Elmore SMR = 1.42; CI = 0.73–2.48; Hazelton SMR = 1.86; CI = 0.85–3.54. Poisson regression analyses controlling for age, race, and calendar period of risk indicated that, in the total cohort, decade of hire had an effect independent of potential latency (time since first employment). The standardized rate ratios (SRRs) for those hired before 1950, hired

TABLE X. SMRs for Lung Cancer at the Reading Plant by Latency and Duration of Employment in Study of U.S. Male Beryllium Workers Employed 1940–1969 and Followed Through 12/31/88

Latency (years)	Duration of employment (years)								Total	
	<1		1–5		5–10		>10			
	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
<15	7	1.17	0	—	2	1.78	0	—	9	0.78
15–30	27	1.38	11	1.30	1	0.44	1	1.03	44	1.17
>30	40	1.42[a]	13	1.41	4	1.32	10	1.33	67	1.40[a]
Total	74	1.38[b]	24	1.15	7	1.08	15	0.94	120	1.24[a]

[a]Two-sided p-value less than 0.05.
[b]Two-sided p-value less than 0.01.

TABLE XI. Beryllium Workers' Lung Cancer Deaths by Plant Worked and Decade of Hire in Study of U.S. Male Beryllium Workers Employed 1940–1969 and Followed Through 12/31/88

Plant	Hired before 1/1/50			Hired 1/1/50–12/31/59			Hired 1/1/60–12/31/69			Total		
	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
1. Lorain	57	33.8	1.69[a]	—	—	—	—	—	—	57	33.8	1.69[a]
2. Reading	92	72.8	1.26[b]	26	18.4	1.42	2	5.8	0.35	120	96.9	1.24[b]
3. Lucky	—	—	—	9	11.0	0.82	—	—	—	9	11.0	0.82
4. Cleveland[c]	12	11.4	1.06	26	19.7	1.32	6	9.6	0.63	44	40.7	1.08
5. Elmore	—	—	—	12	8.5	1.42	3	6.7	0.45	15	15.2	0.99
6. Hazelton	—	—	—	9	4.8	1.86	4	4.6	0.87	13	9.4	1.39
Multiple plants	12	4.74	2.53[a]	1	2.8	0.36	0	0.3	—	13	7.6	1.67
Unknown (QERs)	4	1.74	2.30	2	3.2	0.62	3	1.9	1.57	9	6.8	1.33
Total	177	124.5	1.42[a]	85	68.4	1.24	18	28.9	0.62	280	221.5	1.26[b]

[a]Two-sided p-value less than 0.01.
[b]Two-sided p-value less than 0.05.
[c]St. Clair and Perkins combined.

1950–1959, and hired in 1960–1969 were 2.03, 1.91, and 1.00, with the last category being significantly lower than the first. The SRRs for time since first employment <15 years, 15–30 years, and >30 years were 1.00, 1.08, and 1.19 (no significant differences). Rates by duration of employment showed no trend. Table XII shows the risk of death from "pneumoconiosis and other respiratory diseases" by latency and duration of employment. The SMRs were elevated in all latency categories but were only statistically significant (SMR of 2.29) in the 20–25 year category. Although still elevated, the SMRs decreased in the longer latency periods of 25–30 and 30 or more years.

Table XIII presents the results of SMR analyses using county death rates for comparison. The SMR for the Lorain plant was lower than the SMR based on U.S. rates, but retained statistical significance, while the SMR for the Reading plant was higher than the SMR based on U.S. rates. Summing the observed deaths and expected deaths for lung cancer based on county rates for all seven plant locations yielded an SMR for lung cancer of 1.32 (CI = 1.16–1.49), which was slightly higher than the SMR based on U.S. rates.

In order to evaluate the potential confounding effect of smoking habits on lung

TABLE XII. SMRs for Pneumoconiosis in the Total Cohort by Latency and Duration of Employment in Study of U.S. Male Beryllium Workers Employed 1940–1969 and Followed Through 12/31/88

Latency (years)	Duration of employment (years)								Total	
	<1		1–5		5–10		>10			
	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR	Obs	SMR
<10	2	1.24	1	0.94	1	1.97	—	—	4	1.26
10–15	3	2.24	1	1.11	0	—	1	1.55	5	1.57
15–20	5	2.39	1	0.63	0	—	1	0.76	7	1.28
20–25	6	1.93	5	2.10	1	1.42	7	3.34	19	2.29[a]
25–30	5	1.07	5	2.75	2	2.28	5	1.79	17	1.54
>30	32	1.43	10	1.36	2	0.94	5	1.00	49	1.33
Total	53	1.51[a]	23	1.43	6	1.19	19	1.60[b]	101	1.48[a]

[a]Two-sided p-value less than 0.01.
[b]Two-sided p-value less than 0.05.

TABLE XIII. SMRs for Malignant Neoplasm of the Trachea, Bronchus, and Lung Among U.S. Male Beryllium Workers Employed 1940–1969 and Followed Through 12/31/88, Using County Death Rates (1950–1983) for Comparison

Plant location		Obs	SMR based on county rates	95% CI	SMR based on U.S. rates
City	County				
1. Lorain	Lorain, OH	57	1.60[a]	1.21–2.08	1.69[a]
2. Reading	Berks, PA	120	1.42[a]	1.18–1.69	1.24[b]
3. Lucky	Ottawa, OH Sandusky, OH Wood, OH	9	0.84	0.38–1.59	0.82
4. Cleveland[c]	Cuyahoga, OH	44	1.05	0.76–1.41	1.08
5. Elmore	Ottawa, OH Sandusky, OH Wood, OH	15	1.06	0.59–1.75	0.99
6. Hazelton	Carbon, PA	13	1.50	0.80–2.57	1.39
Sum of 6 locations		258	1.32[b,d]	1.19–1.46	1.26[a,d]

[a]Two-sided p-value less than 0.01.
[b]Two-sided p-value less than 0.05.
[c]St. Clair and Perkins combined.
[d]Total study population (n = 9225, 280 lung cancer); six locations population (n = 8672, 258 lung cancer).

cancer mortality, adjusted SMRs were calculated for the two plants which had a significant excess of lung cancer and for the cohort as a whole (Table XIII). The smoking adjustment factor was 1.1323, which means that smoking alone could account for an SMR of 1.13. When this factor was used to adjust the number of lung cancers expected, the SMR for the Reading plant was 1.09, the SMR for the Lorain plant was 1.49, and the SMR for the total cohort was 1.12 (Table XIV).

Among the 1,192 workers at the Lorain plant, 98 individuals were identified as having had beryllium disease (91 acute, 6 chronic, and 1 of unknown type) from the BCR mortality study file. The Lorain plant had a higher percentage of beryllium disease cases (8.2%) identified from the BCR than any other individual plant (fewer than 2%). Eleven of the Lorain workers with beryllium disease died of lung cancer (SMR = 3.33; 95% CI = 1.66–5.95). Among the remaining 1,094 Lorain workers, there were 46 lung cancer deaths observed (SMR = 1.51; CI = 1.11–2.02).

TABLE XIV. SMRs for Malignant Neoplasm of the Trachea, Bronchus, and Lung After Smoking Adjustment Among U.S. Male Beryllium Workers Employed 1940–1969 and Followed Through 12/31/88

Plant location	Observed	Adjusted expected[a]	SMR
Lorain	57	38.2	1.49
Reading	120	109.8	1.09
Total	280	250.8	1.12

[a]The smoking adjustment factor of 1.1323 for the four plants in the smoking survey was used to adjust the expected numbers of lung cancers for the two beryllium cohort plants shown and the total.

DISCUSSION

The current study found a modest excess of lung cancer (SMR = 1.26) in a cohort of 9,225 workers employed at seven beryllium processing plants. The two oldest plants in the study had statistically significant excesses of lung cancer; the Lorain plant with a substantial excess (SMR = 1.69) and the Reading plant with a more modest excess (SMR = 1.24). The remaining plants had overall SMRs ranging from 0.82 (Lucky) to 1.39 (Hazelton). However, four of the five plants operating in the 1950s had elevated lung cancer SMRs (ranging from 1.32–1.86) among workers hired during that decade.

The current study included four beryllium production facilities not previously studied, the Perkins, St. Clair, Elmore, and Hazelton plants, and had vital status follow-up 12 years beyond prior studies of the Lorain and Reading plants. The Lorain and Reading cohorts were defined and assembled independently of prior studies and therefore our results should not be interpreted as a simple updating.

A limitation of the current study is that no occupational history data, beyond the starting and ending dates of employment at individual plants, were coded. Therefore, the possibility that the inclusion of salaried workers and other nonproduction personnel (with presumably low potential for exposure) in the study cohort may have diluted the observed risks cannot be evaluated. In addition, the study cannot address the relationship of lung cancer risk to degree of exposure or to specific types of beryllium compounds. We are currently reviewing industrial hygiene data from the study plants to determine the feasibility of conducting a nested case-control study to examine lung cancer risk in relation to exposure in more detail. Another limitation of the study is the use of the BCR to identify individuals with a history of beryllium disease. To the extent that all cases of beryllium disease may not have been reported to the registry, the results may overestimate or underestimate the differential lung cancer risk between cases and noncases.

Analyses were conducted to estimate the potential contribution of geographic variation in lung cancer mortality and differences in smoking habits between the study cohorts and the U.S. population to the lung cancer excess. Adjustment for differences in lung cancer mortality by county lowered the SMR for Lorain to 1.61 from 1.69, increased the SMR for Reading to 1.42 from 1.24, and slightly increased the SMR for all seven plants combined (1.32 from 1.26). Counties are the smallest geographic area for which mortality data and population data are routinely available. County referent rates may be preferable to U.S. referent rates if there is substantial regional variability in the diseases of interest. However, the county in which a plant is located may not always provide a better referent population than the U.S., particularly if the county

is predominantly rural and the plant population is drawn primarily from an urban area. In this study, we estimated that 89% of Lorain plant employees were residents of the city of Lorain, while only 26% of Lorain county residents resided in the city of Lorain (as of 1950) [U.S. Census, 1950]. Similarly, we estimate that 68% of Reading plant employees were residents of the city of Reading, while 26% of Berks County residents resided in the city of Reading (as of 1960) [U.S. Census, 1960]. Urban dwellers may smoke more than rural dwellers, and urban areas have been found to have a higher incidence of lung cancer than rural areas [Weinberg et al., 1982]. Thus, while we interpret the results of the county rate analysis with some caution, we conclude that the excess lung cancer mortality observed in this study is unlikely to be due to regional differences in lung cancer risk.

Adjustment for differences in smoking habits between the cohort and the U.S. population decreased the SMR for lung cancer in the overall cohort to 1.12. The major difficulty in interpreting the smoking adjustment is that the smoking data were collected in the late 1960s, while most (94%) of the lung cancer cases occurred among workers hired in the 1940s and 1950s. Thus, the smoking adjustment relies on the assumption (among others) that the difference in smoking habits between the workers and the U.S. population was the same in the 1940s and 1950s as it was in the late 1960s. Examining the SMRs for smoking-related diseases provides some support for increased smoking in the cohort, since emphysema and ischemic heart disease have elevated SMRs (Appendix). However, other investigators have shown that increased smoking is unlikely to account for SMRs above 1.3 for lung cancer and other smoking-related diseases [Siemiatycki et al., 1988].

Increasing duration of employment did not appear to be associated with increased lung cancer risk in the overall cohort; in fact the SMR for individuals employed under 1 year (1.32) is slightly higher than the overall SMR (1.26). Lack of an apparent "dose-response" may reflect the problem in using duration of employment as a surrogate for degree of exposure. The SMR analyses showed a trend of increasing lung cancer SMRs with increasing potential latency, but there was no significant trend for latency in Poisson regression analyses controlling for decade of hire.

The Lorain plant appears to have had a higher excess risk of lung cancer than any other plant in the study, and also appears to have had a higher risk of beryllium disease. Among workers in the Lorain cohort, 8.2% were identified in records of the BCR mortality study; while fewer than 2% of individuals in any of the other plants were identified in BCR records. Most (93%) of the beryllium disease cases were of the acute type, which is associated with very high exposure [Eisenbud and Lisson, 1983]. This suggests that workers at the Lorain plant may have been exposed to higher levels or more toxic forms of beryllium than workers in other beryllium processing facilities. The lung cancer risk at the Lorain plant was higher among 98 workers identified as having had beryllium disease (SMR = 3.33; 95% CI = 1.66–5.95) than among 1,094 workers not known to have had beryllium disease (SMR = 1.51; 95% CI = 1.11–2.02). This pattern within the Lorain cohort is consistent with higher doses of beryllium leading to higher lung cancer risk.

We hypothesized that workers hired during the 1940s might have higher lung cancer risks than workers hired later, because exposures during the 1940s were known to be extraordinarily high. However, in the overall cohort, lung cancer SRRs for workers hired during the 1950s (SRR = 1.91) were not significantly different than lung cancer SRRs for those hired prior to 1950 (SRR = 2.03), when compared

to the group of workers hired after 1960 (SRR = 1.00). Elevated, but not statistically significant, lung cancer SMRs were observed among workers hired during the 1950s at the Reading (SMR = 1.42), Elmore (SMR = 1.42), Hazelton (SMR = 1.86), and Cleveland (SMR = 1.32) plants. Therefore, it does not appear that the excess lung cancer risk in this cohort of beryllium workers is confined to the group who began their exposures at the Lorain and Reading plants in the 1940s.

The study had as a secondary objective to evaluate mortality from nonmalignant respiratory disease, cardiovascular disease, and other causes of death. A significant SMR of 1.48 was observed in the overall cohort for "pneumoconiosis and other respiratory diseases"; a particularly high risk was observed among the small group of individuals (n = 296) identified only from Social Security QERs (SMR = 3.47). The elevated SMR for ischemic heart disease in the entire cohort was largely accounted for by the SMR of 1.12 at the Reading plant, although many of the other plants had SMRs of about 1.00. This finding is unusual in an occupational cohort study where deficits in ischemic heart diseases mortality are generally observed because of the "healthy worker effect" [Monson, 1986]. Only the Lorain plant had a significant excess in the cause-of-death category which includes cor pulmonale, a known complication of beryllium disease.

An excess of "chronic and unspecified nephritis, renal failure, and other renal sclerosis," was also observed. An increase in renal disease has not previously been associated with beryllium in toxicologic or epidemiologic studies. The significant elevation in the SMR for this category of renal disease at the Lorain plant, which probably had high exposures to beryllium and other process chemicals, suggests that the renal disease excess may be occupationally related and should be investigated further. Pathology studies have demonstrated calcific inclusions in the kidneys of individuals with beryllium disease [Freiman and Hardy, 1970]; however, none of the 98 individuals identified as having beryllium disease at the Lorain plant died of renal disease.

In conclusion, the cohort overall and two of the oldest plants (Reading and Lorain) have a significantly increased SMR for lung cancer. Lung cancer was particularly elevated among workers at the Lorain plant with a history of (primarily) acute beryllium disease, which is associated with very high beryllium exposure. The lung cancer excess was not restricted to plants operating in the 1940s, when beryllium exposures were known to be extraordinarily high. Elevated lung cancer SMRs were also observed for four of the five plants operating in the 1950s for workers hired during that decade. Neither smoking nor geographic location fully explains the increased lung cancer risk. An association of beryllium exposure and lung cancer is biologically plausible since a number of beryllium compounds have produced lung tumors by inhalation or intratracheal administration in experimental animals [IARC, 1980]. Occupational exposure to beryllium compounds is the most plausible explanation for the increased risk of lung cancer observed in this study. Continued mortality follow-up of this cohort will provide a more definitive assessment of lung cancer risk at the newer plants and among cohort members hired in the 1950s or later at the older plants. Further clarification of the potential for specific beryllium compounds to induce lung cancer in humans, and the possible contribution of other exposures in specific processes at these plants, would require a nested case-control study. We are currently assessing whether available industrial hygiene data would support such an analysis.

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APPENDIX. Mortality (Through 12/31/88) From Specific Causes Among Beryllium Production Workers

Cause	ICD codes (9th revision)	Obs	Exp	SMR	95% CI
Tuberculosis	010–018	21	24.1	0.87	0.54–1.33
Malignant neoplasms					
Buccal and pharynx	140–149	20	19.8	1.01	0.62–1.56
Digestive organs	150–159	183	181.4	1.01	0.87–1.17
Esophagus	150	23	17.1	1.34	0.85–2.01
Stomach	151	38	32.9	1.16	0.82–1.59
Intestine (except rectum)	152–153	67	60.0	1.12	0.86–1.42
Rectum	154	16	17.8	0.90	0.51–1.46
Liver and biliary	155, 156	9	16.1	0.56	0.26–1.06
Biliary passages, liver, gallbladder	155.0–155.1,156	7	11.0	0.63	0.25–1.31
Liver not specified	155.2	2	5.0	0.40	0.05–1.44
Pancreas	157	27	34.4	0.79	0.52–1.14
Peritoneum and unspecified digestive organs	158,159	3	3.1	0.96	0.20–2.80
Respiratory system	160–165	289	233.8	1.24[a]	1.10–1.39
Larynx	161	7	9.6	0.73	0.29–1.50
Trachea, bronchus, and lung	162	280	221.5	1.26[a]	1.12–1.42
Nasal and other parts	160,163–165	2	2.7	0.74	0.09–2.68
Breast	174–175	3	0.9	3.28	0.68–9.58
Male genital organs	185–187	38	49.1	0.77	0.55–1.06
Prostate	185	35	45.6	0.77	0.53–1.07
Urinary organs	188–189	28	34.1	0.82	0.55–1.19
Kidney	189.0–189.2	10	16.3	0.61	0.29–1.13
Bladder and other urinary organs	188,189.3–189.9	18	17.8	1.01	0.60–1.60
Lymphatic and hematopoietic	200–208	60	60.3	1.00	0.76–1.28
Lymphosarcoma and reticulosarcoma	200	14	10.8	1.30	0.71–2.18
Hodgkin's disease	201	7	6.3	1.12	0.45–2.30
Leukemia and aleukemia	204–208	19	25.0	0.76	0.46–1.19
Other lymphatic or hematopoietic	202,203	20	18.3	1.09	0.67–1.68
Other sites	170–173,190–199	82	82.1	1.00	0.79–1.24
Neoplasms of benign and unspecified nature	210–239	9	9.2	0.98	0.45–1.86
Diabetes mellitus	250	49	44.6	1.10	0.81–1.45
Blood and blood forming diseases	281–289	7	8.1	0.87	0.35–1.79
Alcoholism and mental disorders	290–319	10	19.8	0.50[b]	0.24–0.93
Nervous system diseases	320–337,349–389	25	30.9	0.81	0.52–1.19
Diseases of the heart	390–398,402–404, 410–414,420–429	1,314	1240.1	1.06[b]	1.00–1.12
Rheumatic heart disease	390–398	15	26.2	0.57[b]	0.32–0.94
Ischemic heart disease	410–414	1,094	1017.5	1.08[b]	1.01–1.14
Chronic disease of endocardium	424	4	9.4	0.43	0.12–1.09
Other myocardial degeneration	429.0–429.1	24	22.0	1.09	0.70–1.62

(*continued*)

APPENDIX. Mortality (Through 12/31/88) From Specific Causes Among Beryllium Production Workers (*Continued*)

Cause	ICD codes (9th revision)	Obs	Exp	SMR	95% CI
Diseases of the heart (continued)					
Hypertension with heart disease	402,404	35	41.7	0.84	0.58–1.17
Other diseases of the heart	420–423,425–428	142	123.2	1.15	0.97–1.36
Diseases of the circulatory system	401,403,405, 415–417,430–438, 440–459	281	283.7	0.99	0.88–1.11
Hypertension without heart disease	401,403,405	12	10.7	1.12	0.58–1.95
Cerebrovascular disease	430–438	179	193.2	0.93	0.80–1.07
Diseases of arteries, veins, and pulmonary circulation	415–417,440–459	90	79.8	1.13	0.91–1.39
Respiratory system diseases	460–466,470–478, 480–487,490–519	229	189.4	1.21[a]	1.06–1.38
Influenza	487	4	3.8	1.06	0.29–2.72
Pneumonia	480–486	65	68.2	0.95	0.74–1.21
Other acute infections	460–486	1	1.2	0.81	0.02–4.51
Chronic and unspecified bronchitis	490,491	10	7.6	1.31	0.63–2.41
Emphysema	492	46	34.3	1.34	0.98–1.79
Asthma	493	2	6.0	0.33	0.04–1.20
Pneumoconiosis and other respiratory disease	470–478,490–491, 494–519	101	68.1	1.48[a]	1.21–1.80
Digestive system diseases	520–537,540–543, 550–553,555–558, 560,562–579	115	150.8	0.76[a]	0.63–0.91
Diseases of stomach and duodenum	531–537	10	20.8	0.48[b]	0.23–0.88
Hernia and intestinal obstruction	550–553,560	4	8.0	0.50	0.14–1.27
Cirrhosis of the liver	571	64	77.9	0.82	0.63–1.05
Other diseases of the digestive system	520–579	37	44.0	0.84	0.59–1.16
Diseases of genitourinary system	580–608,610, 611,614–629	51	44.3	1.15	0.86–1.51
Acute glomerulonephritis, nephrotic syndrome and acute renal failure	580,581,584	6	3.6	1.67	0.61–3.62
Chronic and unspecified nephritis, and renal failure, and other renal sclerosis	582,583, 585–587	30	20.2	1.49[b]	1.00–2.12
Infection of kidney	590	5	5.6	0.90	0.29–2.10
Hyperplasia of prostate	600	5	4.3	1.15	0.37–2.70
Other diseases of male genital organs	601–608	1	1.0	1.01	0.03–5.63
Other genitourinary system diseases	588,589,591, 593,595–599	4	8.3	0.48	0.13–1.23
Diseases of the skin and subcutaneous tissue	680–686,690–709	1	2.4	0.41	0.01–2.28
Musculoskeletal diseases	710–739	3	5.3	0.57	0.12–1.65
Symptoms and ill-defined conditions	780–796,798,799	30	36.2	0.83	0.56–1.18

(continued)

APPENDIX. Mortality (Through 12/31/88) From Specific Causes Among Beryllium Production Workers (*Continued*)

Cause	ICD codes (9th revision)	Obs	Exp	SMR	95% CI
Accidents	E800–848, E850–888,E890–949	201	201.1	1.00	0.87–1.15
Suicide and homicide	E950–E978	80	93.9	0.85	0.68–1.06
All other causes	Residual ICD Categories	65	46.1	1.40	1.14–1.73
Certificates not obtained		46			
All cancers	140–208	703	661.5	1.06	0.99–1.14
Total deaths		3,240	3091.6	1.05[a]	1.01–1.08

[a]Two-sided p-value less than 0.01.
[b]Two-sided p-value less than 0.05.