

Estimating Historical Exposures of Workers in a Beryllium Manufacturing Plant

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Background *Beryllium is known to be toxic to the lungs, causing beryllium lung disease and associated with increased lung cancer risk. Airborne beryllium exposures have been monitored since the 1940s. This study describes methods used to measure airborne beryllium concentrations and how historical measurements from a beryllium manufacturing plant were used to estimate workers' exposures in a lung cancer case–control study.*

Methods *Airborne beryllium concentrations had been measured using all-glass impingers, high-volume air filters, and personal respirable and total dust samplers. To provide consistency in exposure estimates over time, measurements collected by the other monitoring methods were converted to approximate the most frequently used high-volume, time-weighted average measurements. Because industrial hygiene measurements were not collected in every year for all jobs throughout the duration of the case–control study, exposure estimates had to be extrapolated from the existing measurements over time and across jobs.*

Results *Over 7,000 historical measurements were available to estimate beryllium exposures of workers over time. Average exposures between jobs varied considerably and exposures for all jobs decreased dramatically between the 1940s and 1970s due to major plant production changes.*

Conclusions *Although error in the exposure metrics for the cases and controls likely occurred due to limitations of the exposure assessment data, the exposure estimates for each job over time provided a reasonable, objective mechanism for categorizing workers by the relative exposures they were likely to have encountered during their tenure. Am. J. Ind. Med. 39:145–157, 2001. Published 2001 Wiley-Liss, Inc.†*

KEY WORDS: *beryllium; retrospective exposure matrix; lung cancer; case–control study*

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Accepted 11 November 2000

Published 2001 Wiley-Liss, Inc.

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INTRODUCTION

Several cohort mortality studies have shown excess lung cancer risk associated with employment in the beryllium processing industry [Mancuso and El-Attar, 1969; Mancuso, 1970, 1979, 1980; Wagoner et al., 1980; Ward et al., 1992], but no prior studies examined the relationship between lung cancer and intensity or form of beryllium exposure. To examine this relationship, we

conducted a nested case-control study within a beryllium processing plant for which detailed job histories and exposure monitoring data permitted estimation of individual exposures.

The plant was one of seven beryllium processing facilities included in the Ward et al. [1992] cohort. This study describes the methods used to develop exposure estimates for each job over time. The results of the case-control study are reported in a companion paper [Sanderson et al., 2000].

Over 40% of the lung cancer cases and 40% of the person-years at risk (PYAR) in the Ward et al. cohort mortality study were accumulated at this plant. The Reading plant was one of the oldest beryllium plants in the US, beginning operation in 1935, and all beryllium production processes except beryllium metal production were represented. The remaining six plants were not selected for study because they either had few lung cancer cases or the work history records and industrial hygiene data were not adequate for constructing exposure estimates.

Background

Production process description

The manufacture of beryllium products began with extraction of beryllium from the ores, beryl or bertrandite. Beryl is a beryllium-aluminum silicate ($\text{Be}_2\text{Al}_2\text{Si}_6\text{O}_8$) containing approximately 4% beryllium metal and has been the primary ore used in U.S. beryllium plants [Breslin, 1966]. The Reading plant used a fluoride process to extract beryllium from ore. Initially, ore was crushed to an average particle size of 3/4 inches. Crushed ore was ground in a wet-ball mill to minus 200 mesh, then mixed with powdered sodium ferric fluoride—cryolite—(NaFeF_6), sodium silicofluoride (Na_2SiF_6), soda ash (Na_2CO_3), and a small amount of graphite in a mix muller [Breslin, 1966; USEPA, 1973; Cabot-Beryllco, 1982].

The mix was formed into small briquettes and sintered at 750°C [Cabot-Beryllco, 1982]. The sintered briquettes were crushed and ground to minus 100 mesh, slurried in water, progressively thickened, and hot-water leached (80°C) through three stages to remove soluble sodium beryllium fluoride (Na_2BeF_4). Sodium hydroxide was added to the leach liquor to precipitate beryllium hydroxide. The precipitated slurry was filtered, dried, and drummed as plant-grade beryllium hydroxide. Beryllium hydroxide was calcined to beryllium oxide in a rotary kiln maintained at 900°C (low-fired).

Beryllium-copper alloy was the primary product of the Reading plant, but beryllium aluminum, nickel, and chromium alloys were also produced. To produce beryllium-copper alloy, beryllium oxide was blended with carbon dust, copper, and dross from previous melts, into arc furnaces

operated at 2,400°C. Prior to pouring the molten metal, solid impurities were skimmed from the melt and recycled as dross into subsequent furnace charges. Master alloy, containing about 4% beryllium, was cast into ingots and sold in this form or subsequently remelted in carbon arc Detroit furnaces or electric induction furnaces with additional copper to produce alloys containing 0.25–2.75% beryllium.

The foundry, rolling, machining, and rod, wire, and extrusion departments were located in a building separate from the beryllium ore extraction, beryllium oxide, and arc furnace departments where the beryllium copper master alloy was produced. In the hot mill area, alloy ingots were cut to the desired length, heated in a furnace, and successively pressure rolled into 0.250 mm gauge flat strands. The rolls were further pressure rolled in the cold mill area to 0.090 mm gauge. To obtain rolls in widths desired by customers, the rolls were cut, welded, and re-rolled in the slitting department. In the rod, wire, and extrusion press area, alloy ingots were heated and extruded or drawn into long rods or bars, and coils of various diameter wire. Following each rolling, extrusion, or drawing operation the alloy product was heated in annealing furnaces and cleaned in nitric acid baths. Specialty products were made from alloy stock in the foundry and machine shop.

History of the plant

The plant opened in 1935 for the purpose of producing beryllium copper alloy ingots—containing about 97% copper and 2.75% beryllium [Beryllium Corporation, 1966]. Beryllium-copper alloy was always the primary product, but the plant has undergone a number of changes over the years. In 1937 the foundry was added to cast ingots into specific beryllium-copper alloy products. In 1938, hot and cold rolling mills and other equipment were installed to convert ingots into mill products. Such necessary supporting services as annealing, hardening, pickling, slitting, straightening, and testing were also provided for the foundry and metalworking departments. In 1940 an extrusion press to form alloy rods and tubes was added. Rolling mills, slitters, and furnaces have periodically been added to increase output, size ranges, and product quality.

In 1959, a major program for installing local exhaust and general ventilation throughout the plant was begun; in 1964, the ore extraction process was shut down, and beryllium hydroxide was shipped in from another plant. These changes were reported to dramatically lower dust levels plantwide. In 1970 the Detroit furnaces were phased out, and electric induction furnaces began operations in a new melt and cast area. The foundry was gradually phased-out through 1975 and finally closed in April 1976. The arc furnace operations, melting and casting of all alloys, and hot mill rolling were stopped in 1992. Only the cold mill,

slitting, rod, wire, and extrusion, annealing, and pickling departments are currently operating at the plant.

METHODS FOR ESTIMATING HISTORICAL BERYLLIUM EXPOSURES

An exposure matrix was developed which provided airborne beryllium exposure estimates for every job lung cancer cases and controls may have held during the entire study period. Personnel data, including detailed work history records, were originally microfilmed in March 1983 to construct the plant cohort for the mortality study; personnel records for all cases and controls employed beyond March 1983 were microfilmed again in March 1995 to update their work histories for the case-control study. Surveys were conducted at the plant in January 1991 and March 1995 to collect beryllium exposure measurement and production process records—particularly records documenting implementation of engineering controls to reduce airborne beryllium concentrations [Sanderson, 1991, 1995]. A file containing the job descriptions for almost all production jobs between 1953 and 1971 was found during these surveys. The

work histories of cases and controls and the plant archives contained over 500 unique job titles in 23 departments. For the purposes of assigning exposure estimates, jobs with similar exposures were grouped reducing to 325 the number of jobs for which exposure estimates were generated.

Historical Industrial Hygiene Data

The company first began to collect beryllium air measurements in 1971; an extensive search was conducted to locate all additional exposure data collected at the plant before this date. Besides company-collected measurements, copies of survey reports and beryllium air sampling data were obtained from other sources (Table I). These records contained beryllium air sampling measurements which were collected using several different methods.

The only beryllium measurements available before 1961 for estimating exposures at the Reading plant were short-term impinger and high-volume filter samples (Table I). These short-term samples represented task-specific exposures or exposures in work areas associated with particular jobs. Only short-term impinger samples had been

TABLE I. Sources of Historical Industrial Hygiene Data for the Reading Plant Beryllium Workers Case-Control Study, USA

Time period	No. samples	Sample description
1947–1953	96	Impinger samples periodically collected by the Bureau of Industrial Hygiene, Pennsylvania Department of Health. Samples were collected at a flow rate of 1 CFM for 15–30 min as close to the working position as possible. Samples were collected in most of the production areas of the plant.
1947	9	Impinger samples collected by the Rochester Laboratory of the Atomic Energy Commission (AEC) during a 1-day survey. Samples were collected at a flow rate of 0.5–1.0 CFM for 5–10 min. Only one or two samples were collected in seven work areas of the plant.
1948	55	High-volume filter samples collected by the Health and Safety Division of the AEC during a 1-month survey. Samples were collected at a flow rate of 0.5 CFM for 1–30 min. DWA calculations using these samples were not reported. Samples were only collected in the beryllium hydroxide and oxide production areas of the plant; no samples were collected in association with beryllium alloy production.
1949–1951	20	High-volume filter samples collected periodically by the Health and Safety Division of the AEC. High-volume filter samples were collected at a variety of flow rates for 1–30 min and used to calculate DWAs. Samples were primarily collected in the vacuum casting area of the plant which was under contract with AEC, although a few short-term high-volume filter samples were collected in the pickling department.
1961	16	High-volume filter samples collected by the Health and Safety Division of the AEC during a 1-week survey. High-volume filter samples were collected and used to calculate DWAs. Measurements were primarily made for workers involved in the extraction of beryllium hydroxide from beryl ore. However, the laundry and laboratory workers were also monitored; no samples were collected in association with beryllium alloy production.
1971–1992	6974	High-volume filter measurements collected quarterly by the industrial hygiene staff at the Reading plant. Short-term high-volume filter samples collected in the workers' breathing zone or general work area were used to calculate DWAs for basically all of the production jobs in the plant. General area samples were collected in office areas, the lunch room, and laboratories.
1972	109 (total) 111 (resp)	Personal total and respirable dust samples collected by the Department of Environmental Resources, Pennsylvania State Health Department over a 3-week period. Both total and respirable samplers were worn simultaneously by workers being monitored. Samples were collected for approximately 6 h from workers in most production jobs.
1975	68	Personal total particulate samples collected over a 2-week period by NIOSH during a Health Hazard Evaluation. A 1-day follow-up survey was conducted to re-monitor workers in the arc furnace area. Samples were collected at a flow rate of 1.5 Lpm over the 8-hour work shift from workers in most of the production jobs.

collected in association with the beryllium alloy production areas of the plant where most employees had worked. All-glass impingers containing distilled water were usually collected at a flow rate of one cubic foot per minute (cfm) for 15–30 min in positions as close to the actual working position as possible in order to allow normal work activities to proceed [Laskin et al. 1950; Shilen et al., 1954].

Expanding production and use of beryllium in the 1940s was closely tied to the development of nuclear power and weapons [Kriebel et al., 1988]. The AEC, which was in charge of the government's supply of materials for nuclear production, set air standards for beryllium production plants after it became obvious that beryllium caused respiratory disease. In 1949, the AEC established an 8-hour time-weighted average (TWA) maximum permissible level of 2 micrograms per cubic meter of air ($\mu\text{g}/\text{m}^3$) and a maximum level of 25 $\mu\text{g}/\text{m}^3$ for workplace air [Eisenbud, 1961]. To enforce these standards the AEC required air sampling at plants under government contract [Breslin and Harris, 1958]. As a result, much of the air monitoring data collected in the beryllium industry since the late 1940s has employed the AEC sampling and analytic technique.

The AEC method involved drawing air through 4-inch Whatman #41 filter paper at a flow rate of 20 cfm for a few minutes during each task workers performed and sampling general workroom air to estimate workers' exposures when not performing specific tasks [Breslin and Harris, 1958; Hiser and Donaldson, 1961]. On the basis of these short-term air samples, a daily average exposure was computed for each job in the plant [Breslin, 1966]. The average exposure was time-weighted by multiplying the average beryllium concentration for each job task or work area, by the amount of time workers in that job spent each day in accomplishing the task or in the work area. The sum of all these products divided by the total length of the workday yielded the daily weighted average (DWA) concentration (Figure 1). The use of the term "daily weighted average" rather than the more commonly used "time-weighted average" emphasizes that the concentrations were derived from short-term samples, weighted on the basis of a time study, instead of from full shift samples [Kriebel et al., 1988].

The impinger and filter samples were analyzed using one of two methods, spectrographic or fluorometric [Cholak and Hubbard, 1948; Walkley, 1959]. Samples were first analyzed for beryllium using the spectrophotometric method in which beryllium formed a red-brown complex with zenia dye [Shilen et al., 1954]. This analytical method generally ceased to be used in the early 1950s. The fluorometric method became the method of choice because it had greater sensitivity and reliability and was a simpler procedure to use, but the two methods were reported to yield similar results.

The impinger and high-volume filter samples collected at the Reading plant between 1947 and 1953 had not

been used to calculate DWA measurements. No comparison studies of impinger and high-volume filter measurements for airborne beryllium have been published. Laskin et al. [1950] did report the simultaneous collection of seven impinger and five high-volume filter samples, indicating that impinger measurements for airborne beryllium were lower than high-volume filter measurements. But for simplicity and in lieu of an accurate conversion factor, the impinger samples were assumed to be equivalent to high-volume filter samples in this study. Other researchers have also assumed impinger and high-volume filter samples to be equivalent when constructing a beryllium exposure matrix [Kriebel et al., 1988].

Personal sampling methods, which measured individual exposures over the entire work shift during all tasks, were not available in the late 1940s when airborne standards for beryllium were proposed. A study had been conducted by NIOSH at another plant to compare the relationship between the AEC sampling method, and personal sampling for total and respirable dust mass [Donaldson and Stringer, 1980]. Total dust mass was sampled with a filter in a closed-face cassette and respirable dust mass was sampled through a cyclone pre-separator to basically collect particles less than about 5 μm in diameter. The personal total dust samples were higher than DWA measurements and respirable dust measurements were lower. The differences between the personal and DWA samples varied by job category, probably because the beryllium particle size distributions varied by job. Since personal sampling methods gave results different from the AEC method, an equation was calculated to convert personal sampling results into a DWA result. A plot of the relationship between the logarithmic means of 21 job-based DWA and total dust measurements is presented in Figure 2. Only 44% of the variability in AEC-DWA samples could be accounted for by linear association with personal total dust samples.

The three types of samplers differ in how they collect airborne particles due to air-inlet differences, electrostatic effects, filter efficiency, and sampling volumes [Cohen et al., 1983]. Also, the beryllium concentrations measured at different positions near a worker's body have been shown to be rather variable [Cohen et al., 1983]. Airborne beryllium particles vary across jobs in their particle size distribution; aerodynamic properties such as shape, form, and density; concentration; and, distribution within the breathing zone and general work area. These differences may partially explain the weak correlation among the samplers.

However, general conclusions may be drawn from comparisons of the DWA measurements to personal total and respirable measurements. Total samples were consistently the highest; because they were located near the breathing zone of the workers, they may more accurately reflect workers' true beryllium exposure, indicating that DWA samples underestimate true exposure. The respirable

BERYLLIUM CORPORATION

Operator: Arc Furnace Helper

OPERATIONS OR OPERATING AREA	TIME PER OPER. [MIN.]	OPER. PER SHIFT	TIME PER SHIFT (MIN.)	NO. OF SAMPLES	CONCENTRATION $\mu\text{g}/\text{m}^3$			AVER. CONC. TIMES TOTAL TIME (T x C)
					LOW	HIGH	AVER.	
Operator's Control Stations #4 Fce GA			21	12	0.22	1.63	0.48	10
Charge Storage Area #4 Fce GA			81	3	0.46	1.97	1.02	83
Charging #4 FCE GA*			32	4	2.00	13.7	6.50	208
Tapping #4 Fce BZ*			43	3	1.01	5.00	2.42	104
Adds Fce Dust & Stirs & Skims Dross BZ*			64	5	2.14	4.29	3.31	212
Drum Dross at Dross Table BZ*			21	3	5.90	9.90	7.19	151
Transfer Metal BZ*			22	2	2.14	8.90	5.52	121
Pouring to Pigs BZ*			43	3	1.33	5.31	3.87	166
Cleans Floor Sweeping BZ*			37	1	4.05	4.05	4.05	150
Bags Charge Mix BZ*			70	2	1.0	4.05	2.52	176
Prepare & Weigh Cu Scrap GA			16	1	0.25	0.25	0.25	4
Lunch			15	3	0.17	2.10	0.84	13
Washup Locker Room			15	7	0.54	8.60	2.25	34

* Respirator Operation

 ΣT 480 $\Sigma(T \times C)$ 1432

$$\frac{\Sigma(T \times C)}{\Sigma(T)} = \frac{1432}{480} = 2.98 \mu\text{g}/\text{m}^3$$

Figure 1. Example of a DWA calculation.

measurements were generally the lowest, indicating that much of the airborne beryllium particulate was unlikely to reach the alveoli of the lungs and would either not be inhaled or would be deposited in the nose or upper airways.

Because beryllium is primarily a lung toxin, the respirable dust measurements may be the most important predictor of lung disease associated with beryllium. However, this association could not be tested in this study because few

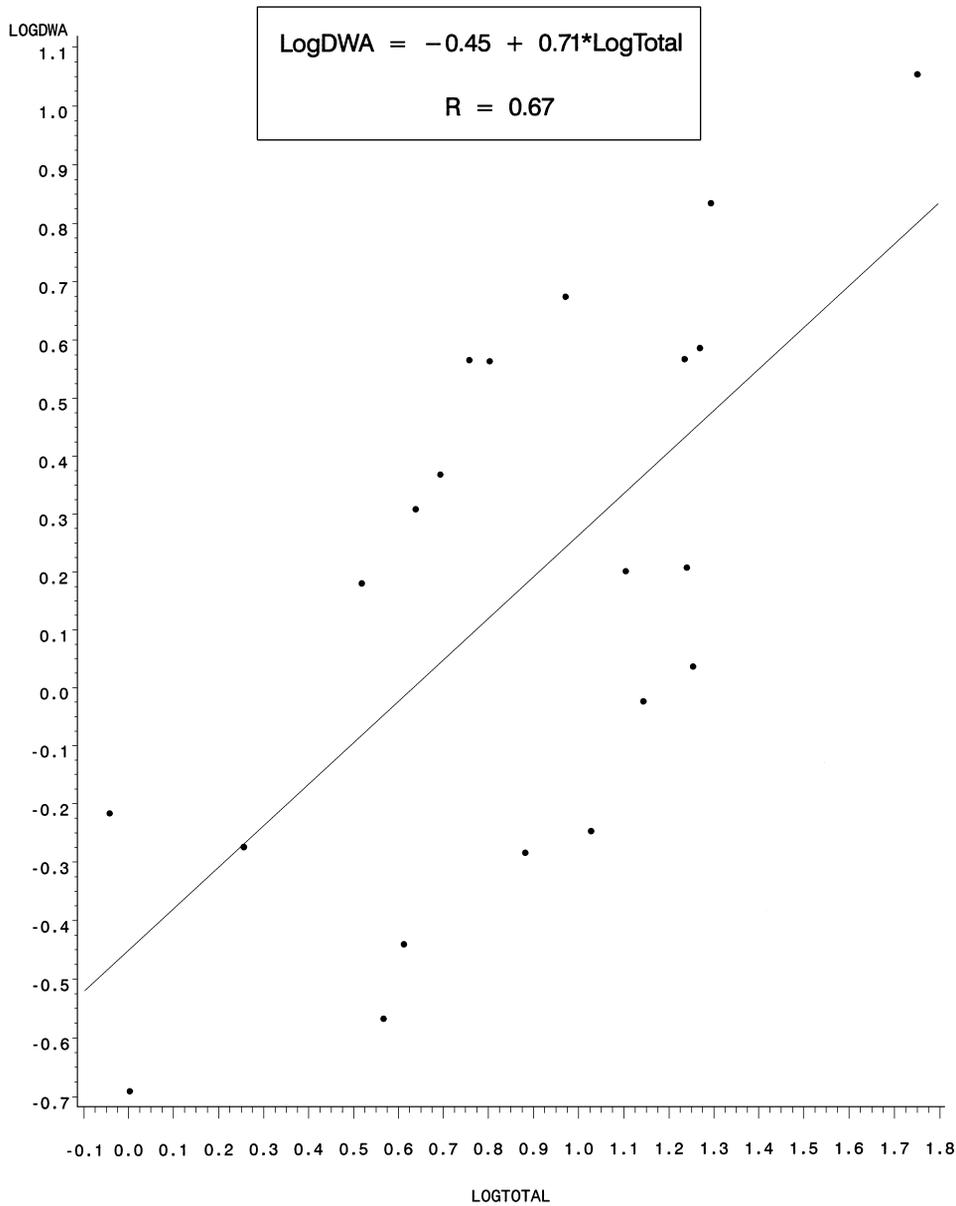


Figure 2. Regression of the log of DWA samples on the log of personal total samples.

respirable dust samples were ever collected at the Reading plant.

Production, Engineering Control, and Job Task Changes

It is not known how constant exposures were in the Reading plant between 1935 when operations began and 1949 when the AEC proposed the $2 \mu\text{g}/\text{m}^3$ occupational exposure limit. The plant may have initiated control measures in response to demands by the AEC; however, the vacuum casting department and perhaps ore extraction

through beryllium oxide production departments were the only work areas which ever operated under AEC contract.

Historical information on production changes and job tasks guided estimation of beryllium exposure levels over time and indicated which jobs had similar duties and therefore similar exposures. Review of the historical measurements collected in the late 1940s and early 1950s supported the conclusion that beryllium exposures remained relatively constant during this time period, except in one area—the Ajax furnace—where reports in the archives indicated that ventilation controls were installed to reduce workers' exposures. But in reality, too few samples were

available to adequately evaluate trends in exposures between 1935 and 1960.

The AEC reported that extensive ventilation and environmental control measures were initiated throughout the entire Reading refinery in 1959 and that before that time only the mixing and sinter furnace areas had any substantial dust control equipment [AEC, 1961]. The AEC survey had not included the beryllium alloy production areas where the Ajax furnace was located. At the time of the survey the ventilation system was only partially installed; the duct work was in place but most of the exhaust hoods were not connected. Many work areas had no dust control, and beryllium aerosol from furnace areas cross-contaminated other departments. Rules concerning the wearing of respirators were generally ignored. This information supports the assumption that exposures throughout the plant may have remained fairly constant between 1935 and 1960. Therefore, with the exception of the Ajax furnace, the impinger and high-volume filter sample data were used to estimate job exposures for all the years between 1935 and 1960. Measurements for the Ajax furnace were stratified to estimate exposures before controls were implemented in 1950 and exposures from 1950 to 1960.

Job-Exposure Matrix Development

Since the majority of the exposure measurements at the Reading plant were DWA measurements, and health effects studies and exposure standards were based on DWA measurements, impinger and high-volume samples were used to calculate DWA estimates. The geometric means of the impinger and high-volume filter measurements, stratified by work area, were used to estimate the expected beryllium concentration that workers would encounter. The arithmetic mean of exposure measurements is often used when summing exposures across years in various jobs, because of its relationship with cumulative dose [Mulhausen and Damiano, 1998]. However, there is no assurance that it would have the stronger relationship with lung cancer risk. Because the geometric mean is lower than the arithmetic mean in a lognormal distribution, the geometric mean underestimates average exposure. The geometric mean is however, less influenced by extreme values in the distribution. Since the number of samples within each stratum was small and the range of concentrations often wide, geometric means, rather than arithmetic means, were used to estimate the expected beryllium concentration to reduce the influence of extremely high measurements.

Since the impinger and high-volume filter samples were short-term measurements associated with specific tasks and work areas, they did not reflect the beryllium exposures workers would experience over the entire workshift. Since the length of time the workers spent in the work areas or performed job tasks was not recorded when these samples

were collected, the estimated duration of various job tasks was taken from DWA measurements collected in later years. Kriebel et al. [1988] applied a similar approach to convert the impinger samples to DWA measurements in their respiratory disease study of workers at the Reading plant [Kriebel et al., 1988].

This method assumes that the time needed to complete the various tasks associated with each job changed little between 1935 and 1961 or 1971. The job descriptions in the plant archives indicated that the production process and job duties remained relatively constant during these years. Where dramatic changes were known to have occurred, the task times were adjusted. However, it is probable that some time changes remain unknown. Also, the DWA method does not account for individual variability in time requirements to complete assigned job tasks or differences in work practices.

No beryllium measurements were available to estimate exposures between 1961 and 1971. Long-tenured employees reported that exposures began to decrease plantwide between 1959 and 1962 when the company installed extensive ventilation controls, although no measurements were available to confirm this. Before this time, fumes from furnace operations cross-contaminated nearby work areas and suspended aerosol was clearly visible throughout many areas in the plant [Sanderson, 1995]. They also reported that housekeeping generally improved plantwide after 1960.

Plant archives and long-tenured employees also indicated that exposures dramatically decreased again after 1971 [Sanderson, 1995]. The Occupational Safety and Health Act became law in 1970 and the workplace exposure standards for beryllium were implemented [Federal Register, 1971]. Before this time most areas of the plant had never been evaluated for compliance with the $2 \mu\text{g}/\text{m}^3$ exposure standard. In 1971, the company and union formed an occupational health and safety committee which made recommendations for improving working conditions, and the quarterly monitoring for beryllium exposures began.

Exposures between 1960 and 1971 were probably lower than pre-1960 exposures but higher than post-1970 exposures. Therefore, the least biased estimates for job exposures during the years 1961 through 1970 were considered to be the midpoint between the jobs' 1960 DWA estimates and the geometric means of the DWA measurements collected by the company during the 1970s.

All job exposure estimates after 1970 were based on the quarterly company-collected DWA measurements ($n = 6,974$). The geometric mean of the DWA measurements collected for a job within a year was used as the expected beryllium exposure concentration of workers employed in that job during that year. If no samples were collected during a particular year, then the midpoint between the years before and after in which DWA measurements had been collected was used as the exposure estimate for that year. Thus, after 1971 annual beryllium exposure estimates were determined

for almost all of the production jobs at the Reading plant. Analysis of variance of the log to these measurements was used to evaluate differences in exposures across jobs and years.

Although most production jobs were represented by at least a few samples, no samples had been collected for some jobs before 1971. To estimate exposures for these jobs, exposure estimates were extrapolated from sample-represented jobs located in nearby work areas or with similar duties. For example, impinger samples were collected in the machine shop in association with lathe operators and grinders, but samples were not reported for other machine shop jobs such as general machinists, drill press operators, and saw operators. Since workers in all these jobs share a common work area and perform similar duties, exposure estimates for all the machine shop jobs were considered to be similar to exposures for the lathe operators and grinders.

In areas of the plant where no samples had been collected, job exposure estimates were based on measurements from other areas of the plant expected to have similar types of exposure. For example, the rod, wire, and extrusion and slitting departments were not represented by any beryllium measurements before 1971. But, these departments were located very near the cold rolling mill where workers performed somewhat similar duties—operating machinery which changed the shape of beryllium alloys. Therefore, exposure measurements from the cold mill were used to estimate exposures for workers in the rod, wire, and extrusion and slitting departments.

No measurements were available for maintenance workers, general laborers, and salaried personnel such as managers, engineers, sales staff, and office workers. Exposure estimates for these jobs were developed by using measurements that most closely reflected exposures for tasks these types of workers would perform. For example, to calculate DWA measurements for janitors who performed housekeeping chores throughout the plant, the company collected short-term high-volume filter samples in a variety of work areas including the office areas of salaried personnel. These short-term samples of the janitors were applied to time estimates of the salaried personnel to calculate their DWA exposures. Because the duties of maintenance workers and general laborers could take them anywhere in the plant, DWA estimates for these workers were calculated by averaging DWA exposure estimates from a variety of production jobs. The personal total and respirable measurements were also used to provide relative ranking of exposure estimates for jobs which were not represented by any DWA measurements.

Workers at the Reading plant were exposed to a variety of beryllium compounds: beryl ore; beryllium fluoride; beryllium hydroxide; beryllium oxide; beryllium–copper alloy; and, beryllium–aluminum alloy. The types of

beryllium compounds to which they were exposed depended upon the jobs and work areas in which they worked. For example, workers involved in extracting beryllium hydroxide from beryllium ore such as mixers, sinter furnace operators, and leachers, would have been exposed to beryllium ore, beryllium fluoride, and beryllium hydroxide. Arc furnace operators would have been exposed to beryllium oxide, beryllium fluoride, and beryllium–copper alloy.

Workers were also exposed to beryllium compounds in two different forms—as a dust or fume. Exposure to fumes was associated with furnace operations where beryllium compounds were heated to high temperatures. Fume particles would tend to be smaller, and therefore more inhalable, than dust particles generated in non-furnace work areas. Workers in some jobs, such as maintenance workers, would have been exposed to both fumes and dust.

The various chemical and physical forms of beryllium possess differing toxicities. Beryllium–copper alloy has been shown to be relatively non-toxic to rat lungs, while beryllium sulfate and beryllium oxide are carcinogenic [Groth, 1980]. The physical form of beryllium determines particle size and thereby ability to reach the lung, and perhaps solubility in lung fluid. To study the association between the various chemical and physical forms and lung cancer, production process descriptions and industrial hygiene survey reports were used to determine the chemical and physical forms of beryllium to which workers would have been exposed in each job at the Reading plant.

Using production process information, the presence of other chemical agents possibly toxic to the lung were determined for each job. Unfortunately, measurements were not available to quantitatively estimate exposure to these agents. Since fluoride extraction was used to refine beryllium ore, workers were exposed to fluorides—which were first believed to be the cause of acute berylliosis and dermatitis—as far down the process as the hot mill area [Shilen et al., 1944, 1954]. Because beryllium was alloyed to other metals, workers in the arc and melting and casting furnace areas were also exposed to copper, and workers in the Ajax furnace area were also exposed to aluminum, chromium, and nickel. Within the pickling area, workers were exposed to nitric acid aerosol and oxides of nitrogen; also within the pickling area a portion of the final beryllium products was plated with cadmium. Some of the maintenance workers performed welding, resulting in exposure to welding fume and gases.

Evaluation of the Job-Exposure Matrix

To evaluate the validity of the exposure matrix, a group of long-tenured employees (some first hired in the 1940s) was asked to review the DWA exposure estimates for every job. The members of the review panel were selected because

they had been employed in the plant over a long period of time and had knowledge of many different work areas and jobs. The panel discussed the production process, changes in the process and job tasks over time, the implementation of environmental controls, and how these changes may have affected job exposures. During these discussions, the panel had access to historical information such as job descriptions, diagrams of the plant, industrial hygiene reports, and reports describing process changes. The panel ranked the work areas and jobs by exposure level. Finally, based on their review and discussion, the panel evaluated plots of the DWA exposure estimates over time for each job. They primarily focused their comments on the exposure estimates for the 1950s and 1960s—time periods about which they had knowledge but for which few exposure data were available. They concluded that the matrix provided reasonable estimates for each job. However, they recommended slightly increasing or decreasing the exposure estimates and altering the points in time at which exposures decreased for some jobs. The review and modification of the matrix were completed without knowledge of which jobs the cases and controls had held. These final, quantitative, time-specific exposure estimates for each of 325 jobs were then linked to the work history records of each case and control to make quantitative beryllium dose metrics.

The total and respirable personal samples collected contemporarily with company-collected DWA samples, were compared and used to adjust the DWA job exposure estimates. For example, personal samples from the furnace and foundry workers indicated somewhat higher exposures than represented by the DWA measurements.

RESULTS

The exposure estimates in $\mu\text{g}/\text{m}^3$ for selected jobs during specific time periods are presented in Table II. Although DWA estimates were calculated yearly from 1971 onward, the geometric mean of the annual DWA estimates for the decades of the 1970s and 1980s are presented for summarization purposes. This table shows that the exposure estimates varied considerably from job to job and that exposure estimates for all jobs were highest in the early years of plant operation declining until 1971. Table II also presents the chemical and physical forms of beryllium, and potential confounding exposures associated with the selected jobs.

The DWA concentrations calculated from the short-term impinger and high-volume filter samples, the AEC DWA samples, and the company-collected quarterly DWA concentrations were plotted over time for each job. These plots were examined for long-term exposure trends. The DWA exposure plots showed that beryllium exposures changed over time, reflecting improvements in environmental controls or changes in the production process. For

example, extensive controls were introduced on the furnaces and conveyors to reduce workers' exposures to beryllium dust and fume between 1976 and 1978. The DWA measurements associated with these work areas declined and remained relatively stable after these controls were completed. Also, the foundry operations were gradually phased out between 1975 and April 1976, reducing cross-contamination of other work areas by the foundry furnaces. Exposures for most jobs declined through the 1970s and remained relatively constant during the 1980s.

Analysis of variance of the 6,974 DWA measurements collected between 1971 and 1992 indicated clear differences in exposure levels between the various jobs ($P < 0.0001$) and from year to year ($P < 0.0001$). Controlling for fluctuations from quarter to quarter did not significantly reduce the random error estimate. This analysis showed that it was important to characterize workers' exposures by the jobs they held and time periods in which they worked.

Using the exposure estimates for jobs over time, three exposure metrics were calculated for each case and control. The first quantitative metric of exposure was the cumulative beryllium exposure received while employed at the Reading plant. This variable was calculated by summing the products of the number of days of employment in each job the workers held times the job exposure estimate for those specific days. The cumulative beryllium exposure metric is calculated in $\mu\text{g}/\text{m}^3$ days. An example of how the cumulative exposure metric was calculated is given in Table III.

Estimates of the relative intensity of exposure were also calculated for each case and control. One metric of intensity was the workers' average exposure; this metric was calculated by dividing the cumulative exposure by the total number of days employed. The average exposure is calculated in $\mu\text{g}/\text{m}^3$. An example calculation of the average exposure is also provided in Table III. An additional metric of intensity of exposure was the maximum or highest DWA estimate for a job that the cases or controls held during their tenure. The maximum exposure metric was made using a procedure similar to that recommended by Checkoway and Rice [1992], in which the exposure history of each worker is determined in a time-specific intensity profile. In the example in Table III, the metric of maximum exposure for this worker was the highest exposure experienced during his tenure, which was $131 \mu\text{g}/\text{m}^3$. The maximum exposure metric allows an assessment of the effect of maximum intensity of exposure, which may be diluted when only a cumulative exposure metric is analyzed.

Cumulative exposure, which was a function of duration of employment, was correlated with tenure ($r = 0.84$). Average and maximum exposure, which are both estimates of intensities of exposure, were also correlated ($r = 0.90$) with each other. However, the average and maximum exposures were not correlated with the duration of employ-

TABLE II. Daily Weighted Average (DWA) Exposure Estimates in Micrograms per Cubic Meter by Time Period, Types and Form of Beryllium, and Potential Confounders Associated with Selected Jobs Beryllium Workers Case–Control Study, USA

Job	DWAs by time period				Types of Be	Form of Be	Confounders
	1935–1960	1961–1970	1971–1980 ^a	1981–1992 ^a			
Ore mill	70.5	8.5 ^b	—	—	Ore	Dust	F, Cryolite
Sinter mixer	21.6	12.5 ^b	—	—	Ore	Dust	F, Cryolite
Sinter furnace	88.4	15.0 ^b	—	—	Ore, BeOH, BeF, BeO	Mixed	F, Cryolite
Leacher	89.6	22.0 ^b	—	—	BeOH, BeF	Dust	F, NaOH
Calcine furnace	82.1	43.9	1.9	1.1	BeOH, BeF, BeO	Mixed	F
Arc furnace	131.0	69.9	3.1	1.4	BeO, BeF, BeCu	Fume	F, Cu
Dross reclaim	29.2	16.1	1.6	0.12	BeF, BeO, BeCu	Mixed	F, Cu
Melt and cast furnace	65.4	34.8	1.1	0.78	BeF, BeO, BeCu	Fume	F, Cu
Heat weigher	23.6	12.5	0.24	0.17	BeF, BeO, BeCu	Fume	F, Cu
Ajax furnace	767/49 ^c	38.4	1.2 ^d	—	BeF, BeO, BeAl	Fume	F, Al
Foundry molder	55.9	24.1	0.63 ^d	—	BeF, BeO, BeCu	Dust	F, Cu
Machinist	23.0	12.2	0.26	0.11	BeO, BeCu	Dust	Machine Oil
Hot mill roller	25.2	10.9	0.37	0.27	BeF, BeO, BeCu	Dust	F
Scarfer lathe	25.2	11.0	0.51	0.29	BeO, BeCu	Dust	F, Cu
Cold roller	14.8	7.8	0.08	0.03	BeO, BeCu	Dust	—
Extrusion press	17.0	9.1	0.32	0.12	BeO, BeCu	Dust	—
Rod grinder	34.0	18.0	0.36	0.08	BeO, BeCu	Dust	Cu
Bulk annealer	17.5	9.3	0.18	0.06	BeO, BeCu	Dust	Cu
Slitter	9.9	5.2	0.10	0.03	BeCu	Dust	Cu
Pickler	13.9	6.0	0.30	0.08	BeO	Dust	Nitric Acid
Lab assistant	4.0	2.4	0.12	0.05	Ore, BeOH, BeO, BeF, BeCu	Mixed	F, Cu, Al, Ni
Inspector	10.0	5.3	0.13	0.04	BeO, BeCu	Dust	Cu
Packer	4.6	2.0	0.10	0.05	BeCu	Dust	—
Maintenance	25.0	13.5	0.82	0.56	Ore, BeOH, BeF, BeO, BeCu, BeAl	Mixed	Nitric Acid, F, Cu, Al, Ni
Launderer	2.5	1.6	0.24	0.06	Ore, BeOH, BeF, BeO, BeCu, BeAl	Dust	F, Cu, Al, Cr, Ni
Engineer	5.0	2.7	0.15	0.03	Be	Dust	—
Secretary	1.7	1.0	0.16	0.03	Be	Dust	—

^aAverage of the DWA estimates for each year cited.^bJob discontinued in 1966.^cFirst estimate for years 1931–1950, second estimate for years 1951–1960.^dJob discontinued in 1976.

ment or cumulative exposure, indicating that high levels of exposure were experienced by both short-term and long-term employees.

Sensitivity analyses were conducted by assigning jobs two and 10 times higher exposure levels before 1946, a time period not represented by any beryllium exposure measurements. This was based on the suspicion that beryllium exposures may have been higher plantwide during World War II and the earliest days of plant operation. These

analyses did not substantially change the results of the case–control comparisons or interpretation of the data.

The number of days of exposure, cumulative exposure, average exposure, and maximum exposure to each of the types of beryllium—beryl ore, beryllium fluoride, beryllium hydroxide, beryllium oxide, beryllium–copper alloy, and beryllium–aluminum alloy—and each form of beryllium aerosol—dust, fume, or mixed—were calculated for each case and control. These exposure metrics were calculated

TABLE III. Example of a Worker's Work History Record and Calculation of Exposure Estimates Beryllium Workers Case—Control Study, USA

Job	Dates employed	No. Days	Time-specific DWA ($\mu\text{g}/\text{m}^3$)	Exposure estimate ($\mu\text{g}/\text{m}^3$ days)
General laborer	Aug. 8, 1947-Oct. 11, 1947	64	25.0	1600
Arc furnace helper	Oct. 11, 1947-Feb. 23, 1948	135	131.0	17,685
Scarfer lathe	Feb. 23, 1948-Nov. 2, 1948	253	25.2	6375.6
Laid-off	Nov. 2, 1948-Mar. 16, 1949	0	0	0
Scarfer lathe	Mar. 16, 1949-Jul. 10, 1950	481	25.2	12,121.2
Extrusion press helper	Jul. 10, 1950-Mar. 17, 1951	250	17.0	4250
Finish mill operator	Mar. 17, 1951-Sept. 1, 1952	534	14.8	7903.2
Total		1,717		49,935

Number of days of tenure = 1,717 days.

Cumulative exposure = 49,935 $\mu\text{g}/\text{m}^3$ days.

Average exposure = 29.1 $\mu\text{g}/\text{m}^3$.

Maximum exposure = 131 $\mu\text{g}/\text{m}^3$.

using the same methods as used to calculate total beryllium exposures, except that job exposures only contributed to the exposure metrics for the various types and forms of beryllium associated with that job.

The number of days that the cases and controls were exposed to chemical agents which might confound or modify the observation of an association between beryllium and lung cancer were also calculated. Because no measurement data were available for these agents, only the number of days could be calculated by counting the total number of days the workers had been employed in jobs which might encounter exposure to the potential confounders.

DISCUSSION

Although more historical industrial hygiene measurements were available for making job exposure estimates in this study than are often available in other studies, the exposure matrix for the Reading plant had several limitations. Perhaps the greatest limitation was the uncertain accuracy of the exposure estimates for the 1940s and 1950s—the time period during which most of the cohort was exposed. Exposure estimates for these years were based on few airborne beryllium measurements and several assumptions were made in using these measurements to estimate job exposures: the impinger measurements were treated as equivalent to high-volume filter samples; short-term impinger and high-volume filter samples were used to estimate full-shift exposures; measurements were extended to make exposure estimates for job categories and work areas in which no samples were collected; and, exposure estimates were extrapolated over long periods of time during which no samples were collected. Misclassification of exposure certainly occurred by extending exposure estimates for jobs and time periods represented by few or no beryllium

measurements at all, limiting the ability of the matrix to estimate workers' true job exposures and accurately stratify them into exposure categories.

Even during the 1970s and 1980s when many measurements were available, sampling was oriented toward jobs, tasks, or work areas. Thus, insufficient personal sampling existed to estimate variation in exposures between individuals or within individuals over time.

The impinger and high volume samples used to estimate DWAs were not size-selective and collected particles too large to be inhaled or able to reach the lower airways and alveoli. Therefore, these measurements only grossly estimate the concentration of inhaled beryllium particles. However, the measurements may correlate well with the true inhalable and respirable exposures and predict risk for disease.

Although some historical information was available on production process changes and the implementation of environmental controls, no measurements were collected to allow precise estimation of how these changes influenced exposure levels. The time of the changes was used to select points in the matrix when exposure levels decreased, but unfortunately the true effect of the changes on exposure level was unknown.

Misclassification of the true exposure of the cases and controls likely occurred due to the limitations of the exposure assessment data. The cases and controls were compared as to whether they had ever worked within specific departments and job categories and by the number of days they had been employed within the Reading plant. Misclassification of ever working within particular departments and job categories, and inaccurate determination of the number of days employed was less likely to have occurred than misclassification of the quantitative beryllium exposure metrics. However, the ever–never and number-of-

days-employed estimates provide little information about the relative intensity of the workers' exposures. Simple analyses of ever–never working in certain job categories do not consider duration of employment in these jobs nor differences in exposure levels over time. Analyses by number of days employed also do not consider differences in exposure level by job category or changes in exposure over time.

Cumulative exposure may be the most meaningful exposure index for “chronic” diseases, which require prolonged, intense exposure for induction. However, short-term or peak exposures may also be important in the cause of long term diseases [Checkoway and Rice, 1992]. The effect of these short-term peak exposures could be masked if only cumulative exposures are studied. Beryllium is known to cause both a chronic and an acute form of lung disease. The acute form of beryllium disease is caused by high concentrations of beryllium, probably in excess of 100 µg/m³ [Breslin, 1966]. In a mortality study of 689 patients with beryllium lung disease, Steenland and Ward [1991] found a significant excess of lung cancer (SMR = 2.0). This excess was more pronounced among workers who had acute beryllium lung disease (SMR = 2.32) vs. those with chronic beryllium lung disease (SMR = 1.57), supporting the conclusion that high, short-term exposures may be a significant risk factor for lung cancer.

The exposure matrix was created blindly, with no foreknowledge as to which jobs and work areas the cases had worked. Therefore, misclassification of exposure metrics should have been non-differential according to health status [Kleinbaum et al., 1982; Heederik et al., 1991]. Nondifferential misclassification will on average produce bias toward the null when continuous exposure indices like cumulative exposure are studied [Copeland et al., 1977; Armstrong and Oakes, 1982; Checkoway et al., 1991].

ACKNOWLEDGMENTS

The authors wish to thank Dr. David Kriebel and Dr. Kyle Steenland for assistance with the development of the exposure matrix; Ms. Lynn Woodside and Mr. Carl Harris for their assistance with data collection; Mr. Fred Shaeff and Mr. John Vitalo for helping us to understand plant operations and task changes for all jobs over the course of the plant's existence; Mr. Bill Ehling for assistance with data coding; Ms. Lih Chang and Ms. Xiudong Lei for assistance with data analysis; and, Karen Sanderson for reviewing and editing the manuscript.

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