

Origins of the Standards for Control of
Beryllium Disease (1947-1949)

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The first of the several types of respiratory tract disease to be observed among beryllium workers was chemical pneumonitis, reported from Europe in the mid-1930s (Gelman, 1936). The disease was then thought to be due to exposure to ions such as the fluorides and sulfates involved in beryllium production, rather than the metal itself. This was understandable at the time, considering the innocuous position of this metal in the periodic table of the elements, and the negative results of early animal exposures (Hyslop *et al.*, 1943).

The acute forms of beryllium disease in the United States were first published in 1943 by Van Ordstrand, who reported that a severe form of chemical pneumonitis was occurring among the employees of beryllium extraction plants in Ohio (Van Ordstrand, 1943). His observations coincided with reports of a chronic form of lung disease in Massachusetts factories that used beryllium in fluorescent lamp manufacturing (Hardy and Taberchaw, 1946).

The first general review of beryllium disease was at a symposium held in September 1947 at Saranac Lake, New York, (Vorwald, 1950). A total of 40 cases of chronic disease, including seven or more deaths and about 500 cases of acute disease, with about one dozen deaths, had by then been reported in the United States. The number of cases was destined to increase in the months ahead.

The Saranac symposium marked a turning point in the history of beryllium disease in two important respects: (a) it was the first time that the complicated pieces of what was then called a "gigantic jigsaw puzzle" (Shipman, 1950) were reported at a scientific conference; and (b) a number of newly developed procedures for the chemical analysis of beryllium in air and tissue samples were presented that made it possible to begin quantitative investigations in the field and laboratory (Durkan, 1950; Poritsky, 1950). The Saranac Lake symposium was also important because it set the stage for intensive field and laboratory studies that were initiated immediately following the conference by the newly formed Atomic Energy Commission.

The field studies were undertaken mainly by the staff of a unit that later became

the AEC's Health and Safety Laboratory, located in New York City.¹ Dr. Leonard Goldwater, then of Columbia University School of Public Health, agreed to undertake an AEC-sponsored case-finding program in the Ohio and Pennsylvania communities where the three U.S. beryllium production plants were located. The University of Rochester also played a key role by undertaking AEC-sponsored animal investigations, by continuing the development of analytical procedures, and by serving as a center for clinical studies.

It soon became evident that the AEC investigations could best be accomplished by concentrating on two Ohio communities, the city of Lorain where the Brush Beryllium Company (now Brush Wellman, Inc.) was then located, and Painesville, Ohio, the site of the former Clifton Products Company. Information from the fluorescent lamp plants in Massachusetts and the large beryllium production facility in Pennsylvania was utilized as it became available, but Ohio had the important advantage that active cooperation was provided by the management of the two companies and the State Health Department under Commissioner Charles Porterfield.²

When the AEC field studies began, it was thought that only the acute forms of beryllium disease had occurred among workers at the production plants. However, by the end of 1947 it was realized that chronic cases had occurred, but had gone unreported due to the general unfamiliarity with the disease that then existed. However, chronic cases were as yet few in Ohio, compared to the much larger numbers of acute cases that had been reported. In contrast, employees involved in the manufacture of fluorescent lamps (as distinct from the preparation of the phosphors used in the lamps) had not experienced the virulent acute chemical pneumonitis seen in the production plants, but an epidemic of chronic disease was well underway. The complexities of the epidemiological pattern as it then existed have been described (Sterner and Eisenbud, 1951).

INVESTIGATION OF THE ACUTE DISEASE

During the first weeks of the field studies it was found that the acute respiratory tract effects being reported were from exposure to beryllium oxide and hydroxide, as well as to the acid salts of beryllium, such as the sulfate, fluoride, and chloride.

¹ The AEC's Health and Safety Laboratory was formed in 1947 and had its origin in the Medical Division of the New York Operations Office. The late Dr. Bernard Wolf, a radiologist, was then Director of the Division, and the writer was Chief of the Industrial Hygiene and Safety Branch, then in the process of formation. When Dr. Wolf retired in 1949, the Medical Division was renamed the Health and Safety Division (later the Health and Safety Laboratory), and the writer was named Director. Christian F. Berghout and A. J. Breslin participated in the early field studies, as did the late W. B. Harris. Harris and Breslin later played major roles in developing the methods by which the stringent standards were to be implemented. The chemical analyses required in support of the field studies were performed by L. T. Steadman of the University of Rochester until the AEC laboratories in New York were completed. The laboratory still exists, but its name has been changed recently to the Environmental Measurements Laboratory and, with the demise of the AEC, it is located within the Department of Energy.

² One of the obstacles in Pennsylvania was the reluctance of the incumbent Commissioner of Health to accept that beryllium was toxic (Shilen *et al.*, 1944). In this respect he was influenced by the U.S. Public Health Service Bureau of Occupational Health, which until late 1949 held to the position that beryllium was of itself not toxic.

However, there was a puzzling inconsistency: workers at the Lorain plant of Brush Beryllium Company who were exposed to high concentrations of beryllium oxide did not develop acute disease, whereas many acute cases had developed, including several fatalities, among employees exposed to the oxide at the Painesville plant of Clifton Products Company. Both plants produced oxides of high chemical purity, and there were initially no apparent differences in their properties.

An inquiry was made of acute cases reported among users of beryllium oxide in the United States and it was learned that, with one important exception, all of the cases of acute disease had been exposed to the oxide produced by Clifton Products. The exception occurred in the laboratory of a large electrical manufacturer, where beryllium oxide was routinely purchased from Brush Beryllium, but a fatal acute case had nevertheless developed. This seemed to assign the then-apparent association of the acute cases with Clifton oxide to the domain of coincidence; but the company industrial hygienist, who was familiar with the progress of our studies, took the time to examine the company's purchasing records and found that Clifton oxide was used for a brief period, during which time the acute case occurred.

Further examination of the comparative properties of the two oxides disclosed that the specific surface area of the Clifton oxide was higher than the Brush product. This was determined to be due to the fact that the Clifton oxide was produced at a lower temperature and, as a result of its smaller particle size and greater specific surface area, was more reactive chemically, and therefore more toxic. Further studies showed that oxides produced above 1540°C do not demonstrate acute toxicity.

This development helped to unravel a mystery in the laboratory as well. The University of Rochester investigators had reported that beryllium oxide was not acutely toxic in rats, but they had been using the Brush oxide. Chemical pneumonitis was produced in the rats when they were subsequently exposed to Clifton oxide (Hall *et al.*, 1950). No "low-fired" beryllium oxide has been produced in the United States since 1948.

Anecdotal evidence was being accumulated from conversations with plant workers and supervisors that cases of pneumonitis were often associated with accidental massive exposure. This was supported by detailed case histories. Confirmation came fortuitously when, in the course of our plant surveys, we found ourselves in a room in which an experimental furnace, during its first test run, suddenly discharged a large puff of a heterogeneous fume consisting of the fluorides of ammonia, magnesium, and beryllium. Air samples collected during the episode made it possible to estimate the concentrations to which eight employees located in the room were being exposed. Within 3 days, three of the employees developed symptoms of respiratory system effects and one of the cases progressed to pneumonitis (Eisenbud *et al.*, 1948).

The importance of short pulses of high exposures led to the realization that it might be necessary to establish two threshold limit values (TLVs) because the limit based on daily weighted average exposures might not be adequate to protect against brief pulses that would be capable of causing acute disease, but would be

of insufficiently long duration to have a significant effect on the daily weighted average required to control the chronic disease.

Since beryllium sulfate was believed to be one of the most virulent beryllium salts, special attention was given to the history of a group of employees who had been working with beryllium sulfate for a long period of time, but who had no history of respiratory illness of any kind. These men had been employed under fairly stable working conditions, and there was little reason to believe that there had been any change in their levels of exposure which, according to our measurements, should not have exceeded $15 \mu\text{g}/\text{m}^3$ of air. The cases we investigated were associated with concentrations greater than $100 \mu\text{g}/\text{m}^3$. It was decided that, for control of the acute disease, a TLV of $25 \mu\text{g}/\text{m}^3$ would be proposed as the maximum permissible peak exposure. It should be noted that this was intended as a *maximum peak* value, rather than a permissible *average* concentration.

In March 1948, about 6 months after the studies began, a progress report was prepared for the use of the Atomic Energy Commission and its contractors (AEC, 1948a), which concluded that

the acute cases seem to be associated with beryllium concentrations in excess of $0.1 \text{ mg}/\text{m}$ of air. We suggest that $0.025 \text{ mg}/\text{m}$ be used as a guide for control of the acute disease. We are not prepared to suggest a safe level for protection against the chronic disease, but it will undoubtedly be much lower than the figure suggested for the acute disease.

The report was presented at the spring meeting of the American Industrial Hygiene Association in 1949, but reference to the TLV for control of the acute disease was omitted from the published paper because of, as recently noted (Hardy, 1980), the objections raised by a consultant to the Commission who was present at the meeting. The recommendation made in the original report was nevertheless sent to all AEC contractors for their guidance (Eisenbud, 1949) and was subsequently adopted by the ACGIH and other organizations; its application has eliminated the acute form of disease.

THE "NEIGHBORHOOD" CASES

Until late 1947, it was not known that cases of chronic disease had occurred in the Ohio production plants, but evidence then accumulated rapidly that such cases existed among both employees and residents in the vicinity of the Lorain plant. One case developed symptoms in 1944, and died in 1946 with a diagnosis of Boeck's sarcoid (AEC, 1948b), a granulomatous lung disease that resembles berylliosis in some respects. The physician who reviewed the history of that case in the fall of 1947 changed the diagnosis to berylliosis, in view of what had been learned about the disease in other parts of the country. The AEC field investigating team, with the knowledge and encouragement of the Brush Beryllium Company, began to canvass the local physicians and gather information about these cases. By July 1948 it was known that at least five cases of chronic disease had developed among former employees of the plant and that eight cases were known among nearby residents who had no history of occupational exposure (Dustan, 1948). The fact that cases had developed in the general community was particularly worrisome. On the initiative of the Brush Beryllium Company, the matter was discussed with Dr. Charles Porterfield, who was then Commissioner of

Health for the State of Ohio, and it was decided that the residents of Lorain should be X-rayed, with provision for further studies of residents with evidence of lung abnormalities. A mass X-ray program was soon undertaken under the direction of Dr. Thomas Mancuso, who was at that time on the staff of the Ohio Health Department. More than 6000 Lorain residents were X-rayed, of whom 12 were recalled for full clinical study. Three additional cases of berylliosis were diagnosed among this group, raising the known cases to 11.

Air sampling in the vicinity of the Lorain plant began in January 1948. The first measurements were made using a mobile sampling station to measure the falloff of atmospheric beryllium downwind from the plant under normal conditions of operation. The concentrations of beryllium were found to decrease from $0.2 \mu\text{g}/\text{m}^3$ at 0.25 mile from the stack to $0.003 \mu\text{g}/\text{m}^3$ at a distance of 5 miles.

Air samples were also collected at several fixed monitoring stations in the vicinity of the plant during 10 weeks of normal plant operation. The first four stations were installed within 700 ft of the plant and a fifth station was established at a distance of 7000 ft to serve as a control.

The results of a 10-week sampling program indicated that the exposures were surprisingly low. Because there was no precedent for believing that such low concentrations of a metal could be responsible for severe pulmonary disease, we were of the opinion that reconstruction of past conditions would reveal that much higher concentrations probably existed. With this in mind, a study was undertaken of the plant operating history to estimate the concentrations that may have existed in past years. Variations could have been due to: (1) the quantity of beryllium being produced; and (2) changes in the method of decontaminating the ventilated air; or (3) other changes in the process.

The Lorain plant began commercial production of beryllium in 1941 and it was found, from examination of the production records, that there had been no great difference in the amount of material processed during the 7 years in which the plant had then been in operation. Production during the peak war years was no more than twice that during the period when our measurements were made.

It was far more difficult to account for changes in the ambient concentrations that might have resulted from changes in the methods of processing exhaust air. At the time of the study, the effluents were being discharged mainly from a 185-ft stack and a number of rooftop stacks approximately 33 ft above street level. Our knowledge of diffusion from point sources was not nearly so well developed then as now, but Sutton had published his classic work the previous year (Sutton, 1947), and Bosanquet and Pearson had published a model in 1936 (Bosanquet and Pearson, 1936). With the cooperation of the U.S. Weather Bureau, an able micrometeorologist, Raymond C. Wanta, was assigned to our project, and he prepared estimates of the relative contributions of pollution from the 33- and 185-ft point sources. Since it was shown that the impact of the 33-ft source was far greater than that of the 185-ft source, it was apparent that atmospheric contamination in the immediate vicinity of the plant, where most of the cases occurred, would have been markedly increased in the past if a greater portion of the atmospheric water had been discharged from roof level (about 33 ft), rather than from the 185-ft stack.

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An effort was then made to reconstruct the relative contribution from emissions from the two levels. Fortunately, the plant records were well maintained, and it was possible to obtain a layout of the plant ventilation system as well as a list of dates when changes in the ventilation system were made. The volume of air and quantity of beryllium being exhausted from each operation were measured along with the collection efficiency of the dust separators. The records showed that the plant effluents had been reduced from time to time by the installation of various kinds of dust collectors and that, over the operating history of the plant, the quantity of beryllium discharged from the 33-ft level was gradually reduced by connecting individual vents to the 185-ft stack. It was estimated that prior to 1944, the rooftop discharges totaled 5000 g/day, compared to 1700 g/day from the 185-ft stack. By the time the studies were conducted in early 1948, the rooftop effluents had been reduced to 1200 g/day, and the 185-ft stack effluents to 2300 g/day. On the basis of this information, it was concluded that the concentrations in the past were higher, but by no more than a factor of 8, than the concentration measured during the 10-week air-sampling period. This factor allowed for increased production as well as for greater roof effluent (Eisenbud *et al.*, 1949).

By late 1948, a total of 11 nonoccupational cases had been diagnosed and located with respect to the plant as summarized in Table 1. The next step was to reconstruct the 7-year exposure history of each of the 11 cases. Interviews with the survivors and their families disclosed that 10 of the cases lived within 0.75 mile from the plant and that no members of their households had worked in the plant. However, the husband of the eleventh case, located at a distance of nearly 1.75 miles had worked in the plant for 3 months, and during this period had brought his work clothes home daily, for laundering by his wife. To simulate such exposure, 100 coveralls worn for 1 day by employees of this plant were obtained, and air samples were collected during the home laundering process. Those were days when modern washing machines were not available, and the procedure required that the clothes be shaken, hand scrubbed, hung to dry, shaken again, and folded. It was found that exposure to the employee's wife was, on average, greater than air-pollution exposure to the residents who lived close to the plant (Eisenbud *et al.*, 1949). It was accordingly concluded that the 10 cases within 0.75 mile from the plant were caused by air pollution, but that the case living 1.75 miles from the

TABLE 1
DISTRIBUTION OF THE NEIGHBORHOOD CASES IN MID-1948

Distance from plant (miles)	No. of cases
0 to ¼	5
¼ to ½	3
½ to ¾	2
¾ to 1	0
1 to 1½	0
1½ to 2	1
Over 2	0

(Eisenbud *et al.*, 1949).

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plant was due to handling contaminated work clothes. On this hypothesis, it became important to estimate the average concentration to which people at a distance of 0.75 mile had been exposed, since this could serve as the basis for establishing an ambient air quality standard.

Wind direction and wind speed data were available from a nearby Coast Guard station for a period covering the plant's operating history. The vertical temperature gradient was measured by equipment installed when our study began. Using the estimated emission rates from the 33- and 185-ft levels during the period when air samples were collected, the observed concentrations were found to be in reasonable agreement with those predicted by diffusion theory. This permitted interpolation between the one station located 7000 ft from the stack and the three stations located within 700 ft of the stack. In this way, it was estimated that during the 10-week test period, the average concentration of beryllium at a distance of 0.75 mile ranged between 0.004 and 0.02 $\mu\text{g}/\text{m}^3$. It was concluded that 0.01 $\mu\text{g}/\text{m}^3$ was a satisfactory approximation of the average 0.75-mile concentration during the period of study. When the increased production rates of the past were taken into consideration, and allowance was made for the much greater discharges from the 33-ft level, the concentrations were estimated to have been greater in the past by approximately a factor of 10. Using this line of reasoning, it was concluded that the lowest exposure that produced disease was greater than 0.01 $\mu\text{g}/\text{m}^3$ and probably less than 0.1 $\mu\text{g}/\text{m}^3$. The factor of 10 was reasonable in view of the operating history of the plant, but a factor of 100 was impossible since this would have required that the discharges to the atmosphere be considerably greater than the amount of beryllium produced.

On the basis of these studies, it was recommended that the concentration of beryllium in community air be maintained below 0.01 $\mu\text{g}/\text{m}^3$ (Eisenbud *et al.*, 1949). It was noted that most of the offending beryllium in this case came from the 33-ft level, from which several thousand grams per day were being discharged for a considerable period of time. Emissions of this magnitude are possible only in the vicinity of a major production facility. The studies also emphasized the importance of avoiding exposure of family members via contaminated work clothes. The recommended standard was widely adopted by regulatory agencies and has now been adopted as a U.S. Environmental Protection Agency air quality criterion. It was the first ambient air quality standard, and preceded all others by about 25 years.

THE OCCUPATIONAL TLV

By mid-1948 a few cases of chronic disease were found to exist among employees or past employees of the Brush Beryllium Company. No cases were reported from the Painesville plant, where a high incidence of acute disease was known to be prevalent.³ There was no discernible pattern in the occupational histories of the Lorain cases. Most of the then-known cases of chronic disease

³ At this writing, about 30 years after the Painesville plant was closed, there is no record of a chronic case having occurred. Recent inquiries among physicians familiar with beryllium disease in the Painesville area disclosed the possible occurrence of one case, but details are lacking.

were from the fluorescent lamp industry in Massachusetts, but no air analyses were available.

In a 1961 review of the problem of setting a standard for control of the chronic disease, I described the dilemma faced in 1948 as follows:

There was not then, nor is there today, any substantial body of environmental information that could be correlated with clinical reports of occupational berylliosis, and such data as do exist are puzzling. In the vicinity of the Lorain plant, a clear-cut relationship between the severity of exposure and the frequency of disease was demonstrated. The people living near the plant had a higher incidence of chronic disease than people living at a distance from the plant, and beyond a certain distance there were no additional cases. . . . However, inside the plant, the people who were exposed to much higher concentrations had a lower frequency of disease and, oddly, some of these cases were of the quasi-occupational type, which included secretaries and others who had only casual contact with beryllium. (Eisenbud, 1961)

The late Willard Machle was then actively involved in beryllium studies, that regrettably remain unpublished, in the fluorescent lamp industry. In consultation with him, it was decided, in late 1948, that because of the absence of an epidemiological basis for establishing a TLV, we would start with the assumption that beryllium was as toxic as some of the heavy metals, such as arsenic, lead, and mercury. However, since the heavy metals have atomic weights of about 200, and since beryllium has an atomic weight of 9, the TLV would have to be reduced by a factor of about 20 relative to the heavy metals. Since the heavy metal TLVs in those days were about $100 \mu\text{g}/\text{m}^3$, this rationale suggested that when corrected for differences in molarity, the TLV for beryllium should be about $5 \mu\text{g}/\text{m}^3$. However, we thought that an additional safety factor was warranted because of the severity and apparent irreversibility of berylliosis, and we decided to recommend $2 \mu\text{g}/\text{m}^3$ on a tentative basis.

DISCUSSION

The above studies covered a period of about 2 years. The three recommended standards were adopted for the tentative use of the AEC contractors in late 1949 (Eisenbud, 1949). An advisory committee of AEC consultants and staff was assembled to review the rationales on which the proposed standards were based and supported the recommendations, but suggested initially that the standards should be *revoked* and *reevaluated* at the end of 6 months. This had the effect of requiring that the information be updated so that justification for these standards could be reviewed. At the end of the first 6-months period, all available data were again reviewed, on the basis of which the tentative standards were extended for 1 year. The committee reconvened annually for several years, and agreed each time that the original standards should be continued. The committee was disbanded⁴ after 8 years, when it became apparent that no new information was being accumulated, and that there was no reason to invalidate the original recommendations.

These standards have now existed for more than 30 years, and they have been adopted by various standards-setting organizations, including the American Industrial Hygiene Association, the American National Standards Institute, and the

⁴ At various times the following served as members of this committee: Harriet Hardy, who was chairwoman throughout; W. B. Harris; Harold Hodge; Robert A. Kehoe; James Sterner; Philip Drinker; B. S. Wolf; and Merrill Eisenbud.

American Conference of Governmental Industrial Hygienists. The Environmental Protection Agency adopted the $0.01 \mu\text{g}/\text{m}^3$ concentration as an ambient air quality standard in 1973. In 1972, NIOSH recommended in its beryllium criteria document that the AEC recommendations for control of occupational exposure be retained in any newly promulgated OSHA standard. Nevertheless, in 1975, OSHA published its proposed provisions in the beryllium standards, based primarily on the assumption that beryllium is a human carcinogen. Their proposals were evaluated at length at hearings in 1977, but no changes have been made as of this writing. This 6-year delay between promulgation of a revised beryllium standard and its (as yet) nonissuance symbolizes the differences that have taken place in the past three decades. Thirty years ago, collaboration between a Federal agency, the beryllium industry, and a state health department led quickly to standards that eventually controlled beryllium disease. There existed at that time a high degree of epidemiological confusion, no lack of differences of opinion, and many technical difficulties. We did not realize it at the time, but it was an experience that was not to be soon repeated.

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Risks of beryllium disease related to work processes at a metal, alloy, and oxide production plant

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Abstract

Objective—To describe relative hazards in sectors of the beryllium industry, risk factors of beryllium disease and sensitisation related to work process were sought in a beryllium manufacturing plant producing pure metal, oxide, alloys, and ceramics.

Methods—All 646 active employees were interviewed; beryllium sensitisation was ascertained with the beryllium lymphocyte proliferation blood test on 627 employees; clinical evaluation and bronchoscopy were offered to people with abnormal test results; and industrial hygiene measurements related to work processes taken in 1984-93 were reviewed.

Results—59 employees (9.4%) had abnormal blood tests, 47 of whom underwent bronchoscopy. 24 new cases of beryllium disease were identified, resulting in a beryllium disease prevalence of 4.6%, including five known cases (29/632). Employees who had worked in ceramics had the highest prevalence of beryllium disease (9.0%). Employees in the pebble plant (producing beryllium metal) who had been employed after 1983 also had increased risk, with a prevalence of beryllium disease of 6.4%, compared with 1.3% of other workers hired in the same period, and a prevalence of abnormal blood tests of 19.2%. Logistic regression modelling confirmed these two risk factors for beryllium disease related to work processes and the dependence on time of the risk at the pebble plant. The pebble plant was not associated with the highest gravimetric industrial hygiene measurements available since 1984.

Conclusion—Further characterisation of exposures in beryllium metal production may be important to understanding how beryllium exposures confer high contemporary risk of beryllium disease.

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Keywords: beryllium; occupational lung disease; lymphocyte proliferation test; surveillance; exposure-response

Beryllium exposure leads to cell mediated immunological sensitisation in a small percentage of workers exposed to beryllium aerosols, dusts, or fumes; of the sensitised workers, many

have granulomatous lung disease.¹⁻³ Prevention of beryllium disease depends on knowledge of risk factors which can be modified. Although inborn genetic factors are associated with risk of disease in those exposed to beryllium,⁴ these cannot be changed in an existing workforce exposed to beryllium. In contrast, work related risk factors offer the opportunity to lower risk of beryllium disease and to understand the exposure characteristics associated with high disease rates. In our previous studies of plant workforces exposed to beryllium, we found risks of beryllium sensitisation or disease related to work processes in three plants representing single sectors of the beryllium industry. These include machining of beryllium metal,¹ grinding, dicing, and drilling of beryllia ceramics,² dry pressing, and research and development in a plant which manufactured beryllia ceramics historically.³ We report here the results of epidemiological and exposure surveillance in a plant which encompasses most sectors of the beryllium industry in production of beryllium metal, alloys, and beryllium oxide from which ceramics were made historically. We sought to describe risks of beryllium disease related to work processes which could provide opportunities for future study of exposure variables conferring excess risk. Understanding of qualitative and quantitative exposure-response relations is critical to prevention of disease in the many sectors of the beryllium industry.

The plant opened in 1953 to produce beryllium-copper alloy, which is cast and fabricated into tubes, wire, sheet, plates, and metal parts before shipment to other factories to become finished products. Beryllium metal operations were developed in about 1957 in buildings and under management which were largely separate from alloy operations. Beryllium metal is produced from beryllium hydroxide through a chemical process. The two component areas involved in beryllium metal production are the pebble plant, which contains fluoride and reduction furnaces, and vacuum melting.³ As the crystalline structure of cast beryllium metal is unsuitable for many applications, the metal is partitioned into differing grades of powder and pressed into metal shapes. A machine shop grinds and finishes many of the cast and pressed beryllium and alloy parts.

The plant also reclaims scrap beryllium and alloy metal and began production of Albemet, a beryllium-aluminum alloy, in 1990. Histori-

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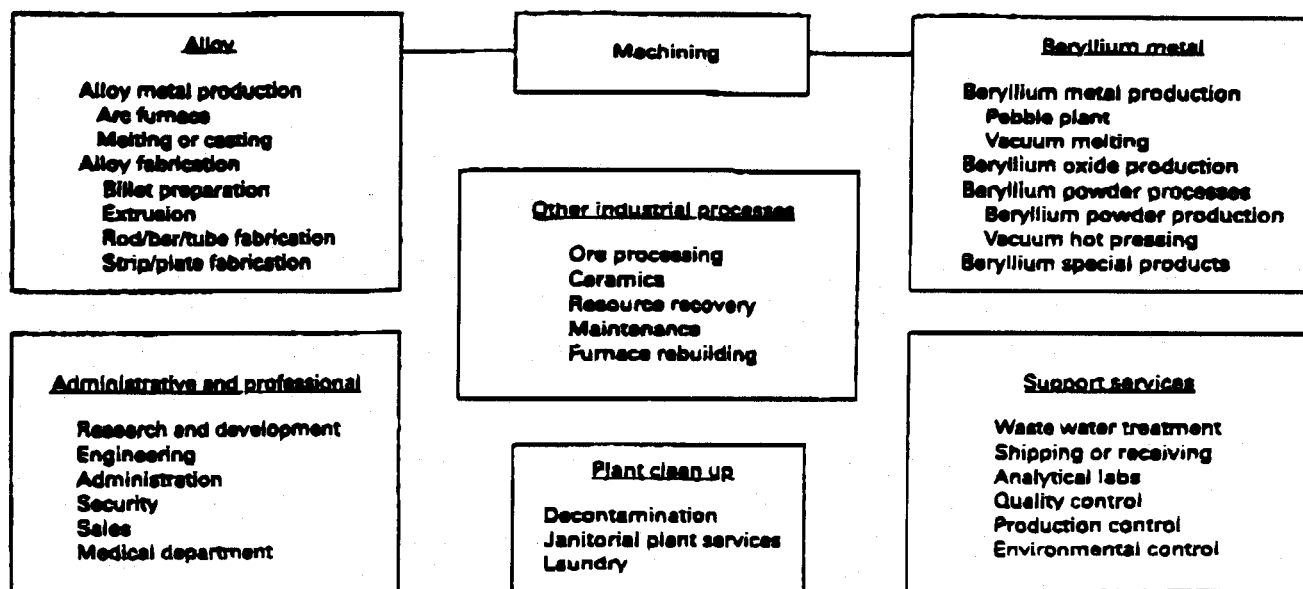


Figure 1. Process classifications and their subgroups used in work history analysis for risks related to work processes and cumulative exposure estimates.

cally, the plant produced beryllium hydroxide from ore until 1972. Beryllium oxide for ceramics has been produced since about 1958 at the metal side of the plant. Beryllia ceramic products were produced at the plant until the operation was moved to another factory between 1980 and 1984. Production of beryllium pebbles in metal production increased coincidentally during a similar period, doubling in 1979, declining to baseline, and then doubling again in 1983-4.

Methods

POPULATION

We invited all 655 employees on the plant roster during the screening period to participate in screening for beryllium disease after presenting information sessions to each workshift. Five employees had already had a diagnosis of chronic beryllium disease. The management at the plant required all current employees to be interviewed during work time over a 13 month period. The screening blood test for beryllium sensitisation was voluntary.

QUESTIONNAIRE

The personnel department provided employees with their work histories for review before confidential interviews with non-plant personnel. Trained interviewers administered an abbreviated standardised respiratory questionnaire,⁶ supplemented with additional medical and work history questions (before blood test results were available) usually within two months of drawing blood. For data analysis of work history, jobs were classified by the individual and grouped processes (fig 1).

BLOOD LYMPHOCYTE PROLIFERATION TEST

After written informed consent, employees gave a 40 ml blood sample collected in heparinised vacutainer tubes, half of which was sent by overnight courier to one laboratory and half to another laboratory for the beryllium lymphocyte proliferation (BeLP) test.⁷ Split

blood samples were collected weekly over a 15 month period from late February 1993 to June 1994. Repeat testing of abnormal and indeterminate results extended blood collection to October 1995.

CLINICAL EVALUATION

Participants with confirmed abnormal BeLP results or with one abnormal result and an indeterminate result during the study were offered clinical evaluation after additional informed consent, including bronchoscopy for bronchoalveolar lavage BeLP test and trans-bronchial lung biopsy. People with an initial abnormal blood test that was not confirmed on two subsequent split tests were not referred for clinical evaluation but were offered repeat blood tests after the study. We defined beryllium sensitisation as a repeatable abnormal BeLP test. We defined beryllium disease as granulomas on lung biopsy in the presence of beryllium sensitisation or an abnormal bronchoalveolar lavage BeLP test.⁸

HISTORICAL INDUSTRIAL HYGIENE DATA

We reviewed all computerised industrial hygiene measurements of beryllium mass concentration ($n=124\ 600$) collected from 1980 to 1993 without regard to particle size or respirable fraction. We excluded 10 080 special samples without location codes and 8322 samples that could not be classified as general area, full shift, breathing zone, or lapel samples, most of which were taken between 1980 and 1984. General area samples ($n=30\ 872$) were collected with high volume samplers for 30 minutes in the work area of specific processes. Continuous samples ($n=59\ 360$) were also collected, usually over a full workshift or occasionally over 24 hours. Process breathing zone samples were collected for 1-15 minutes with high volume samplers ($n=15\ 787$). Beginning in 1990, personal lapel samples ($n=179$) were collected with a monitoring pump positioned on the worker's lapel for the entire work shift for 20 different jobs.

We estimated daily weighted average (DWA) exposures for a working day with formulas incorporating quarterly average general area, continuous area, and breathing zone measurements based on time studies for most jobs. The DWA formulas were added or changed over the years as jobs changed and were available only since 1984 for most production jobs. In alloy areas, only jobs at the arc furnace, the melting-casting furnaces, and some strip-plate operations had DWA formulas. In beryllium metal areas, almost all jobs had DWA formulas. The DWA formulas were not available for jobs in quality control, engineering, decontamination, janitorial, production control, environmental control, administration, security, waste water treatment, and the medical department. We recreated quarterly DWA estimates for individual jobs and job categories with the available formulas and industrial hygiene measurements. If no quarterly measurements existed for a procedure code of a DWA formula, we used measurements from the nearest available quarter to complete the estimate. We created DWAs with existing general area and continuous area sample measurements for workers in alloy rod-bar-tube areas, engineering administration, offices, sales, and waste water treatment. We could not create DWAs for quality control, decontamination, plant cleaning services, production control, environmental control, and security job titles. As these jobs involved tasks in all parts of the plant and in the administrative areas, we assumed that exposure was the average of DWAs for all other jobs during the quarter. We estimated cumulative beryllium exposure for study participants who started employment after 1983 by summing the quarterly DWAs for their job titles, weighted by days of employment in the job title during the quarter, accounting for reported time away from work. The proportion of person-days for which we had job specific DWAs was 90.5%, with the remaining 9.5% being the all plant average DWA estimates. We calculated average beryllium exposure by dividing cumulative exposure, expressed in $\mu\text{g}/\text{m}^3\text{-days}$, by the total number of days worked.

The beryllium detection limit for all industrial hygiene samples was $0.1 \mu\text{g}/\text{m}^3$, but the industrial hygiene database did not distinguish between samples below or at the detection limit. For the purpose of DWA analyses, we recoded all 0.1 measurements as $0.05 \mu\text{g}/\text{m}^3$.

CUMULATIVE INCIDENCE

The plant medical department supplied names and dates of hire of 24 former employees diagnosed with chronic beryllium disease before the cross sectional screening. The plant management provided us with a count of unique employees by year of hire, with which we calculated a minimum cumulative incidence.

STATISTICAL ANALYSIS

The five current employees carrying a diagnosis of chronic beryllium disease were included as cases in most analyses. We excluded them from the analyses of chest and dermatological

symptoms and workplace risk factors as they answered these questions after knowing their diagnosis. The prevalent cases were included in work history analysis until their date of diagnosis.

We analysed questionnaire and laboratory results with PC SAS, using χ^2 , Fisher's exact test, Student's *t* test, and Wilcoxon's rank sum test, as appropriate. We chose a probability of 0.05 for significance. For logistic regression (PROC LOGISTIC in PC SAS), we used variables from the univariate analyses that were associated with beryllium disease or abnormal BeLP test with a statistical significance of <0.25 and tested the assumption that the logit was linear in the continuous variables. We used stepwise selection with a P value criterion of <0.05 to determine which variables and possible interaction terms should be included in the final model.

Data on industrial hygiene were left censored due to the detection limit of $0.1 \mu\text{g}/\text{m}^3$ and did not fit a normal or a log normal distribution. We used medians, ranges, and quartiles to describe these data. We compared groups with Wilcoxon's rank sum test, χ^2 test, and Fisher's exact tests. We compared the mean of the personal lapel samples for each job title within a quarter to the corresponding quarterly DWA estimates with Wilcoxon's sign rank test and Spearman's correlation coefficient.

Results

DEMOGRAPHIC DATA

Of the 655 employees invited to participate, 646 (98.6%) completed the interview, the rest having left employment, retired, or died before interview. Most employees were male (85.1%) and non-hispanic white (94.7%). The mean age was 43.9 years, with a range of 24 to 61. Average employment at the plant was 17.6 years, with a range from seven months to 38.3 years. Employees changed work processes an average of 9.4 times throughout their employment (range 1-50), but were employed on an average of only 4.4 different processes (range 1-15).

BLOOD BERYLLIUM BeLP TEST RESULTS AND CLINICAL CLASSIFICATION

Excluding the five employees with a diagnosis of beryllium disease, 627 (97.8% of those interviewed) had blood drawn for the BeLP test. Fifty people had a confirmed abnormal blood test from either one or two laboratories or had a combination of an abnormal blood test and indeterminate test (table 1). Forty seven of the 50 underwent clinical evaluation. Twenty had granulomas on biopsy in the presence of beryllium sensitisation, and four others had abnormal bronchoalveolar lavage BeLP tests and no granulomas. Of these four people, one had a 29% lavage lymphocytosis with multinucleated giant cells and no history of cobalt exposure; one had 31% lymphocytes and fibrosis on biopsy; and the other two had 19% and 46% lavage lymphocytes. Three of the four had rebiopsy without obvious granulomas about one year after initial bronchoscopy, and the fourth had a granuloma on rebiopsy.

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Table 1 Clinical evaluation results of employees with abnormal blood test results

Seroing category	n	Clinically	Beryllium	Sensitized to beryllium
		evaluated	disease	test without disease
		n	A	n
Confirmed abnormal in both laboratory	15	14	9	6*
Confirmed abnormal in one laboratory	16	16	10	6
Initially abnormal with indeterminate result	19	17	9	3
Initially abnormal with normal result	9	0	—	4†
Total	59	47	24	19

* One of those classified as sensitized to beryllium but without disease did not undergo clinical evaluation.

† Six of nine employees were retested in the autumn of 1995, allowing four to meet the definition of a case of sensitization; disease has not been excluded.

The remaining 23 people did not have beryllium disease documented by biopsy or lavage BeLP test abnormalities; however, three had increased lavage lymphocyte proportions of 22%, 27%, and 37%.

Nine people had initial abnormal blood tests, retested normal on two subsequent tests, and were not offered clinical evaluation. Six of the nine had follow up blood testing in the autumn of 1995, four of whom had abnormal BeLP test results confirming beryllium sensitization.

PREVALENCE OF BERYLLIUM DISEASE, SENSITIZATION, AND ABNORMAL BLOOD TEST

The prevalence of abnormal blood BeLP tests was 9.4% (59/627), excluding previously diagnosed cases of beryllium disease as they did not have blood tests as part of this study. The prevalence of beryllium sensitization was 6.9% (43/627), again excluding the known cases of disease. The prevalence of beryllium disease, including previously diagnosed cases in the current workforce, was 4.6% (29/632). Twelve people with abnormal blood tests did not have clinical evaluation required for classification as beryllium disease.

ASSOCIATIONS BETWEEN DEMOGRAPHIC DATA AND CHRONIC BERYLLIUM DISEASE

We compared the 24 new cases of beryllium disease and the five previously diagnosed cases with all employees with normal blood test results. The 29 cases with beryllium disease were significantly younger than others at age of diagnosis (39.2 v 44.0 years, $P=0.005$). They did not differ significantly from the remainder of study participants in sex, race, ethnicity, cigarette smoking, pack years of smoking, or time since first employment. Cases of beryllium disease had time since first employment ranging from 1.8 to 27.5 years. No significant differences existed in chest or dermatological (rash, ulcer, or delayed healing of cuts) symptoms between new cases of beryllium disease and those with normal blood tests. Of the five previously diagnosed cases of disease, one reported a usual cough and phlegm, four reported wheezing occasionally apart from colds, and two reported having to walk more slowly than people of their age on the level because of breathlessness. Patients with beryllium disease were no more likely than normal people to report having been in an accident

or unusual incident that may have resulted in high beryllium exposures (58.3% v 53.9%, $P=0.67$).

ASSOCIATIONS BETWEEN WORK PROCESS AND CASES OF BERYLLIUM DISEASE

We assessed possible beryllium exposure-response relations by comparing prevalences of work processes in cases and normal people and by comparing disease prevalence by working groups. The 29 disease cases were more likely than those with normal blood tests to have worked in ceramic fabrication (48.3% v 24.1%, $P=0.004$). In assessing prevalence of disease among employees in different work processes, we controlled for overestimates of risk by removing employees who worked in ceramics from the prevalence estimates for other processes (table 2). When we looked at grouped processes, we found that cases worked in beryllium metal production (pebble plant and vacuum melting) more than normal people (51.7% v 34.2%, $P=0.05$). Two cases of beryllium disease had worked only for purchasing or accounting. Another had worked only in alloy maintenance.

As many employees without ceramic exposure had started working after ceramics production stopped in the plant, we examined whether the increased risk of beryllium disease among ceramic employees was attributable to secular trends in exposures or latency. When we restricted the analysis to all employees who began working before 1984 (last date of ceramic fabrication work), a significant difference remained in the prevalence of disease, 9.3% (14/150) in ceramics workers compared with a prevalence of 3.9% among workers never in ceramics ($P=0.025$). Beryllium metal production was not associated with significantly increased prevalence, even when ceramics workers were removed from the analysis.

Conversely, we looked at all employees who began working after ceramics work was moved from the plant ($n=190$) and found an 8% prevalence (4/50) in beryllium metal production compared with a 0.7% prevalence (1/140) among employees in all other processes ($P=0.02$). Looking at the two process areas in beryllium metal production, those employees working in the pebble plant had a 7.3% prevalence (3/41) compared with a 1.3% prevalence (2/148) among other employees ($P=0.07$), and employees working in vacuum melting had a 13.3% prevalence (2/15) compared with 1.7% (3/175) among people in all other processes ($P=0.05$). Six employees had worked in both the pebble plant and vacuum melting, of whom one had disease. The prevalences of beryllium disease among all pebble plant workers and vacuum melting workers hired after 1983 were 6.4% and 12.5%, respectively.

Logistic regression analysis reflected the univariate analyses. We included 12 demographic and workplace variables in the creation of our model: sex, race, smoking status, pack years of smoking, time since first employment, work in another beryllium facility, work around beryllium fluoride, pebble plant, vacuum melting, alloy extrusion, ceramics, and shipping or

*Beryllium disease surveillance***Table 2** Adjusted prevalence of beryllium disease and abnormal blood BeLP test by work process

Process	At risk (n)	Beryllium disease*	Abnormal blood test*
Ceramics	193	9.0	11.6
Beryllium metal production†	193	5.2	14.2
Pebble plant‡	134	5.2	13.4
Vacuum melting§	21	4.8	19.0
Shipping or receiving¶	17	3.9	5.9
Furnace rebuild	21	0	4.8
Office work	65	3.1	7.7
Beryllium powder processing**	47	2.1	6.5
Maintenance	104	2.9	11.3
Engineering research and development	33	1.9	7.7
Alloy metal production	69	4.3	5.8
Alloy melting or casting	65	4.6	6.2
Analytical laboratory††	25	4.0	20.0
Alloy arc furnace	18	0	0

*Prevalences are based on all employees at risk and do not match prevalence comparisons in the text, which were made with employees with normal blood count.

†All employees who ever worked in ceramics which have been removed from these groups.

‡All employees who have ever worked in ceramics or the pebble plant have been removed from these groups.

Table 3 Logistic regression model of variables predictive of beryllium disease

Independent variable	Estimated coefficient	OR (95% CI)	P value
Beryllium disease model:			
Intercept	-3.7172	—	0.0001
Ceramics history	1.4790	4.39 (1.83 to 10.50)	0.0009
Pebble plant	3.1561	23.48 (4.39 to 123.32)	0.0002
Years since first employment	-0.0016	1.00 (0.99 to 1.05)	0.9569
Pebble plant x years since first employment	-0.1764	0.84 (0.75 to 0.94)	0.0025

*This model cannot be used to accurately measure risk for pebble plant employment as time since first employment is a continuous variable and cannot be inverted at the high and low end of the continuum. This is an unavoidable problem when a continuous covariate is modeled linearly in a logistic. This does not affect the risk estimates for ceramics.

receiving. We did not include beryllium metal production (the grouped process of pebble plant and vacuum melting) to find which of the two processes was contributing to the increased risk. We also included possible interaction terms. Four variables were included in the final model (table 3): ceramics, work in the pebble plant, time since first employment, and an interaction term between time since first employment and the pebble plant. The odds ratio (OR) of beryllium disease for people working in ceramics was 4.4. Work in the pebble plant interacted with time since first exposure and reflects the previous analysis in which beryllium metal production was a risk factor since 1984. The model predicts that pebble plant work conferred no additional risk for a person with employment of 17.6 years but a 5.7-fold risk for someone first employed in 1985.

ASSOCIATIONS BETWEEN DEMOGRAPHIC DATA, WORK PROCESSES, AND ABNORMAL BLOOD TESTS

We compared the 35 employees with abnormal blood tests but without documented beryllium disease with those employees with normal blood tests. People with abnormal blood tests were no different in age, sex, race, smoking status, pack-years of smoking, or time since first employment. There were also no significant differences in chest or skin symptoms, although those with abnormal blood tests (but without disease) were more likely than those with normal blood tests to report having their job changed due to a rash (36.0% v 13.6%, $P=0.007$), and were more likely to have had a rash within the month before interview (28% v

3.8%, $P=0.008$). No difference existed between the two groups in reports of having been exposed to beryllium in an accident or unusual incident.

People with abnormal blood tests were more likely than people with normal blood tests to work in the analytical laboratory (17.1% v 5.5%, $P=0.02$). Restricting the analysis to people employed before 1984, the association with the analytical laboratory remained (22.7% v 6.5%, $P=0.02$). For people employed after 1983, employees with abnormal blood tests only were more likely to have worked in the pebble plant (46.2% v 20.5% among others, $P=0.04$); the prevalence of abnormal blood tests among pebble plant workers, including cases of beryllium disease, was 19.2% v 5.8% among others.

We included 16 variables and possible interaction terms in the creation of our logistic regression model for abnormal blood BeLP test (but without beryllium disease) and only work in the analytical laboratory entered the model with an OR of 3.6.

HISTORICAL ENVIRONMENTAL MEASUREMENTS (1984-93)

Full shift and continuous area samples ($n=59$ 360) had a median (max) beryllium concentration of 0.6 (1290) $\mu\text{g}/\text{m}^3$. The 30 872 general area samples had a median (max) of 0.4 (2615) $\mu\text{g}/\text{m}^3$. The 15 787 breathing zone samples had a median (max) of 1.4 (3750) $\mu\text{g}/\text{m}^3$; and exceeded 5 $\mu\text{g}/\text{m}^3$ in 18.5% of samples and the peak exposure limit of 25 $\mu\text{g}/\text{m}^3$ in 3.6% of samples. The 179 personal label samples had a median (range) of 1.0 (0.1-52.6) $\mu\text{g}/\text{m}^3$.

Median general area measurements in different work areas ranged from 0.1 to 0.7 $\mu\text{g}/\text{m}^3$ with alloy arc furnace and alloy melting-casting areas having the highest median value and the arc furnace having the highest percentage (15.0%) of measurements over the 2 $\mu\text{g}/\text{m}^3$ standard. Median breathing zone samples ranged from 0.1 to 2.0 $\mu\text{g}/\text{m}^3$, with beryllium powder and laundry areas having the highest median values and furnace rebuild having the highest percentage (28.6%) of measurements over the short term exposure limit of 5 $\mu\text{g}/\text{m}^3$.

Quarterly DWA estimates were available for 18 process areas (based on our groupings in fig 1) for 40 quarters in 1984-93. Some process areas had multiple jobs with DWA estimates. Quarterly job specific DWAs ranged from 0.05 to 63.11 $\mu\text{g}/\text{m}^3$, with alloy arc furnace workers and furnace rebuild workers having the highest median DWA estimates at 1.65 $\mu\text{g}/\text{m}^3$ and 1.63 $\mu\text{g}/\text{m}^3$, respectively. These two job descriptions also had the highest percentages of DWA estimates over the 2 $\mu\text{g}/\text{m}^3$ standard, 38% and 40% respectively.

Jobs characterized with personal label samples had one to seven measurements per quarter in 1990-92, with beryllium oxide production, alloy melting and casting, and the arc furnace having the highest median label sample measurements (3.80, 1.75, and 1.75 $\mu\text{g}/\text{m}^3$, respectively) and the highest percentages of samples over the 2.0 $\mu\text{g}/\text{m}^3$ standard (64.3%, 47.2%, and 44.4%, respectively). Analysis of

Table 4. Pebble plant exposures from 1984 to 1993

Exposure assessment method	n	Median ($\mu\text{g}/\text{m}^3$)	> 2 $\mu\text{g}/\text{m}^3$ as personal standard ^a (%)	Range ($\mu\text{g}/\text{m}^3$)
Control area measurements	13796	0.4	6.4	0.1-79.2
Breathing zone measurements	1496	1.1	11.0	0.1-293.3
Daily assigned average	225	0.7	6.0	0.1-7.9
Lapel samples (1988-2)	60	0.9	27.3	0.2-19.0

^a Beryllium standard for short term exposure limit for breathing zone measurements is 5 $\mu\text{g}/\text{m}^3$.

average personal lapel samples and corresponding quarterly DWA estimates for 103 pairs of samples showed that lapel samples tended to be significantly higher than the DWA estimates with a median (range) difference of -0.19 (-27.2 to 47.8) $\mu\text{g}/\text{m}^3$ ($P=0.06$, Wilcoxon's sign rank test). The paired data had a correlation coefficient of 0.26.

Estimates of individual cumulative beryllium exposure based on quarterly job specific DWAs were available for 201 people beginning employment after 1983 and before 1994. Individual median (range) cumulative exposures was 1528.1 (1.5-5971.9) $\mu\text{g}/\text{m}^3$ -days for the workforce after 1983. The median (range) average beryllium exposure of the workforce was 1.0 (0.01 to 2.66) $\mu\text{g}/\text{m}^3$.

EXPOSURES ASSOCIATED WITH HIGH RISK WORK PROCESSES

As those employed in the pebble plant after 1983 had excess beryllium disease and abnormal blood BeLP tests, we examined exposure measurements and estimates for pebble plant processes (table 4). Samples were coded as to whether or not a respirator was used while performing the work task. Of all breathing zone samples in the pebble plant, 54.4% were coded as respirator samples compared with 57.0% of samples in all other areas combined. Of lapel samples in the pebble plant, 43.2% were coded as respirator samples compared with 39.4% of lapel samples in other areas.

ASSOCIATIONS BETWEEN EXPOSURE, BERYLLIUM DISEASE, AND ABNORMAL BLOOD BELP TESTS

Cases of beryllium disease among employees employed since 1984 ($n=5$) had a median cumulative beryllium exposure of 1635 $\mu\text{g}/\text{m}^3$ -days and a median average exposure of 1.3 $\mu\text{g}/\text{m}^3$. They did not differ significantly in these exposure indices from normal people (median cumulative exposure 1518 $\mu\text{g}/\text{m}^3$ -days, $P=0.47$ and median average exposure 1.0 $\mu\text{g}/\text{m}^3$, $P=0.27$). No significant difference existed between those with abnormal blood tests without disease ($n=13$) and normal people for cumulative exposure (median for employees with abnormal blood tests=2153 $\mu\text{g}/\text{m}^3$ -days, $P=0.32$) or average beryllium exposure (median for abnormal blood samples=1.3 $\mu\text{g}/\text{m}^3$, $P=0.22$). The percentages of days of work with estimated DWAs (rather than job or location specific DWAs) for cases of beryllium disease, employees with abnormal blood tests, and normal people were 0.5%, 3.6%, and 10.5%, respectively.

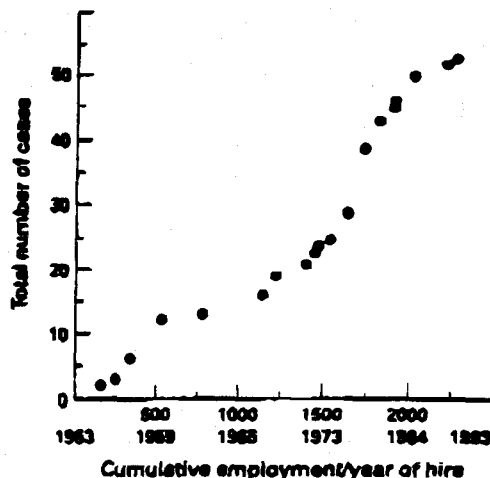


Figure 2. Cumulative number of cases of beryllium disease by cumulative number of people employed at the year of hire.

CUMULATIVE INCIDENCE OF BERYLLIUM DISEASE IN THE PLANT

The minimum cumulative incidence of beryllium disease among the 2274 people ever employed at the plant since it opened in 1953 is 2.3% (53/2274), with little secular variation in rate when cases are plotted by cumulative number of employees at the year of hire (fig 2).

Discussion

RISK OF BERYLLIUM DISEASE

This cross sectional study of an aging workforce, with historical experience in most segments of the beryllium extraction and production industry, showed the highest prevalences of beryllium sensitisation and disease of any large worker cohort which has been systematically screened.¹⁻³ Past ceramic workers in this workforce had high rates of abnormal blood tests (11.6%) and beryllium disease (9.0%) compared with other workers. These prevalences were about double the rates found among ceramics workers in the modern plant to which ceramics work was relocated (5.9% for beryllium sensitisation and 4.4% for beryllium disease) and resembled the rates found among the machinist subgroup of ceramics workers at highest risk in that new plant (14.3% beryllium sensitised and 10.2% with beryllium disease).² Among employees who started working after ceramics operations had been moved out of the plant, pebble plant workers in beryllium metal production had high prevalences of abnormal BeLP tests (19.2%), beryllium sensitisation (14.9%), and beryllium disease (6.4%) compared with others. The high rates of abnormal blood tests only and sensitisation only in this group with 10 years maximum employment may reflect an incomplete latency period for beryllium disease arising after sensitisation. The possibility remains that the risk of disease among people sensitised to beryllium differs by work process.

Despite our findings of excess risk of beryllium disease for ceramics and pebble plant workers, employees in non-production jobs had some risk of beryllium sensitisation and disease, as in other cohorts.¹⁻³ Employees who had worked only in alloy operations also

had some risk, which is of interest for the many workers exposed to beryllium-copper alloy in user industries. However, alloy operations confer substantially less risk of beryllium disease than beryllium metal production and ceramic operations, despite higher indices of exposure to beryllium in alloy production.

The time dependence of the risk of beryllium disease in the pebble plant is of particular interest in the light of a major United States Department of Energy research and development effort in the early 1980s to optimise beryllium production at this plant. Pebble plant processes, which were formerly out of control from an environmental point of view, including the fluoride furnaces, reduction furnaces, and melts crusher, were thought to have been brought under control in the first half of the 1980s.¹ These efforts coincided with a transient doubling of 1979 pebble production in 1980, repeated in 1983-4. Despite considerable improvements motivated to achieve better environmental control, the risk of beryllium disease in the pebble plant increased among beryllium metal production workers hired after 1983, a finding which has also been found for workers hired after 1979 (data not shown). This epidemiological finding suggests that indices used to evaluate exposure of workers have been misleading with respect to the risk to workers of beryllium disease.

EXPOSURE-RESPONSE OBSERVATIONS

Industrial hygiene measurements, available for the period in which the pebble plant conferred excess risk, did not document higher indices of exposure than lower risk processes. This finding contrasts with the only other surveillance study with usable historical measurements, in which the high risk process of ceramic machining was associated with higher industrial hygiene measurements and DWA estimates than were low risk processes.² In the modern ceramics plant, indices of exposure in machining were similar to the same indices for the modern pebble plant, as were the rates of sensitisation (14.3 v 14.9) and disease (10.2 v 6.4).

Risks of beryllium disease or sensitisation related to work processes either reflect exposure factors which confer biological risk or occur by chance alone. The degree of excess risk of beryllium disease conferred by ceramics and the pebble plant are unlikely to have occurred by chance alone. For ceramics workers in this plant, the prevalence of disease is credible, as their rates of disease and sensitisation were similar to the prevalences of the high risk subgroup in the plant to which ceramics operations moved. For pebble plant workers, the period of excess risk of having an abnormal blood test alone coincided with the period with excess risk of disease, making chance a less plausible explanation for the two outcomes in the pebble plant.

The historical measurements may misclassify biologically pertinent exposure in at least three ways. Firstly, DWAs seem to be a poor estimate of personal exposure, as lapel samples correlated weakly with corresponding quarterly

DWA estimates, and lapel samples tended to be higher than the DWA estimates. Secondly, particle size or other characteristic may be more important contributors to risk than is gravimetric measurement without regard to respirability. Thirdly, the methods of beryllium exposure assessment may poorly reflect actual exposures from accidents, which historically often required evacuations in the pebble plant. We found no evidence that respirator use was associated with jobs in the pebble plant, eliminating personal protective equipment as a confounder of exposure characterisation.

The dissociation of high disease risk in the pebble plant from indices of exposure could be interpreted as evidence against an exposure-response relation. We think that the limits of the historical exposure data make such a conclusion premature. Rather, risk related to a work process which can be currently studied, as in the pebble plant, provides an opportunity to use different methods of exposure assessment which may be more pertinent to biological risk. Comparison of exposure variables in the pebble plant, such as respirable mass, particle number, surface area, and solubility, can be made with low risk processes in this and other plants. Understanding of characteristics of sensitising exposures for beryllium disease may be paradigms for other hypersensitivity diseases, such as occupational asthma.

MISCLASSIFICATION OF SENSITISATION

This surveillance study had the strength of complete interview data on all active employees and nearly complete lymphocyte proliferation data on those employees not known to have beryllium disease. However, the study had several limitations which have resulted in likely misclassification of beryllium disease and sensitisation status. Misclassification of these outcomes of interest may have arisen in laboratory tests and clinical evaluation practices.

The two laboratories conducting BeLP tests on split blood samples produced strikingly inconsistent results, both between laboratories and within laboratories on repeat samples. Our definition of beryllium sensitisation required two abnormal tests separated in time, for comparability with previously published surveillance studies.^{1,2} However, these abnormal test results were often accompanied by normal tests in the same or different laboratory. Of the subset of abnormal cases which could not be confirmed in two split repeat tests in the first 17 months of the study, most of those retested at least 16 months later had a second abnormal test. Cases of beryllium disease occurred in the group with unconfirmed abnormal blood tests, and no difference in rate of beryllium disease existed among those with abnormal tests confirmed in one laboratory compared with those with abnormal tests in both laboratories. Thus, our definition of beryllium sensitisation seems overly restrictive for epidemiological purposes, and we are likely to have missed cases of beryllium disease among those people with abnormal tests not referred for clinical evaluation, many of whom with time met the study criterion for diagnostic evaluation. Certainly,

the use of two laboratories led to the identification of more cases of beryllium sensitization and disease than would have occurred with either laboratory alone, a finding that limits the comparison of rates found for this population with some previously published rates.¹ Use of either laboratory alone (first blood test abnormal and confirmation on subsequent test) would have allowed identification of only 46.5% of the cases of sensitization from one laboratory and 48.8% from the other.

In the face of laboratory insensitivity in finding beryllium sensitization, we chose to present results for those ever having an abnormal blood BeLP test. Although some employees with one abnormal BeLP test among several may have had false positive results, the theoretical likelihood of a false positive is about 0.06%; this is based on having two stimulation indices (among six in a test) above the mean plus two SDs for the peak stimulation index of unexposed people.

UNDERESTIMATION OF BERYLLIUM DISEASE

It is likely that this study has underestimated rates of beryllium disease because of three practices in clinical evaluation. Firstly, not all people with abnormal blood tests underwent clinical evaluation, precluding any possibility of making a diagnosis of beryllium disease. Secondly, the lavage BeLP test protocol used by the clinical laboratory for this study used three beryllium concentrations on harvest day 4, by contrast with three concentrations on harvest days 3 and 5 used in other published studies.^{1,2} As well as this change in protocol, less than three concentrations of beryllium were used in most tests, which is likely to have resulted in lowered sensitivity for detecting an abnormal lavage BeLP test.

Thirdly, the biopsy practices in the clinical evaluations may have resulted in underestimation of disease. The average number of biopsies taken in those undergoing bronchoscopy was four, which is considerably lower than the customary 8–12 biopsies taken in previously published work.^{1,2} In sarcoidosis, the rate of granulomatous abnormalities increases with increasing number of biopsies,¹⁰ and this seemed to be the case in those undergoing bronchoscopy in this study (data not shown). Although we have documented that granulomas can precede abnormal lavage BeLP tests,¹ the authors from the National Jewish Centre have invariably found granulomas in those with abnormal lavage BeLP tests, although a second bronchoscopy has occasionally been necessary. Rebiopsy of three cases with abnormal lavage BeLP tests but no granulomas in this study did not document granulomas, although all three cases had other evidence of pathological abnormality—such as lymphocytic alveolitis or fibrosis. Only future follow up will clarify whether we have classified them correctly as having beryllium disease. Their exclusion from analyses did not change the risk factors which we have presented here.

A final limitation of this cross sectional study is a healthy worker effect, which would lead to an underestimation of rates of beryllium

disease. New cases of beryllium disease identified in this surveillance effort had not come to clinical attention, and only five previously diagnosed cases were still working in the plant. We know that some cases of sensitization to beryllium progress to subclinical beryllium disease,^{1,2} and that some of these progress with the passage of time to be clinical cases. The younger age of cases of beryllium disease compared with people with normal blood tests is best explained by the possibility that clinical cases of beryllium disease from this plant have left employment, and the remaining subclinical cases are unrepresentative of the age distribution of the plant population.

IMPLICATIONS FOR FUTURE SURVEILLANCE

Efficacy is unknown for interventions after early identification of beryllium sensitization and disease—such as removal from exposure or early treatment. In this context, the main justification of screening is scientific investigation of risk factors and of natural history. Understanding of risk factors can lead to effective primary prevention. Understanding of natural history of beryllium sensitization, perhaps in concert with genetic risk factors,³ can lead to consideration of intervention trials and appropriate policy for secondary prevention. This surveillance study has laid the groundwork for both efforts in the production sectors of the beryllium industry and many client sectors of the industry. The most important priority for further investigation is exposure-risk relations, which will serve as the basis for primary prevention throughout the beryllium industry and may have paradigmatic importance for other common lung hypersensitivity diseases, as well.

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