12. BERYLLIUM

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1. What industries and jobs involve beryllium exposure?

Beryllium is an extremely lightweight metal (atomic weight of 9) that is transparent to x-rays and gives up neutrons. These properties led to its use as a lens in x-ray machines and in nuclear weapons as a neutron moderator. As a 1–2% alloy of beryllium-copper, it confers properties of strength, resistance to fatigue and impact, and freedom from deformity due to strain (elastic drift). Thus, beryllium-copper is used in springs and scientific equipment. Beryllium oxide (beryllia) is used to make ceramics, which are excellent heat conductors and high-temperature insulators; hence, beryllia ceramic chips are metallized with circuits for many semiconductor applications, including ignition switches in automobiles.

Industries using beryllium or its compounds include the primary production industries, high-technology ceramics, and alloys for special applications in nuclear weapons, aerospace, dentistry, golf clubs, and tools. Within these industries, virtually all job descriptions may involve beryllium exposure. In addition, beryllium exposure may occur but be unsuspected in reclamation of precious metals.

Exposure in the primary extraction industry involves soluble beryllium salts, and the fumes in extraction furnace operations appears to confer high risk of sensitization and disease in comparison with other processes in metal and alloy production. Elsewhere in the industry, exposure primarily involves dust or beryllium aerosols, as in machining of beryllium-copper alloy, beryllium metal, or beryllia ceramics. Machining processes have been shown to confer excessive risk in both metal and ceramic segments of the industry. Approaches to exposure control include enclosing operations with exhaust ventilation and provision of respiratory protection.

2. What diseases does beryllium cause?

The principal target organs for beryllium-related health effects are the skin and lungs. When workers are exposed to beryllium or its compounds, a small percentage develop granulomatous lung disease, known as chronic beryllium disease. In the beryllium extraction industry, a large percentage of workers develop contact dermatitis and/or beryllium skin ulcers in relation to soluble salt exposure. Historically, workers in extraction also were described as having chemical nasopharyngitis, tracheobronchitis, and/or pneumonitis with subacute onset, which resolved with cessation of exposure to beryllium salts and always within 1 year of symptom onset. In contrast, the chronic disease may develop after workers have left the beryllium industry, sometimes with a latency of several decades from first exposure. With workforce screening, latencies as short as a few weeks from first employment have been recognized.

3. What is Salem sarcoid?

In the 1940s, beryllium oxide was used in making phosphors in the fluorescent light industry before its health hazards were recognized in the United States. With the entry of many women into the workforce during World War II, several cases of severe "sarcoidosis" occurred among young women in a light bulb plant in Salem, Massachusetts. This cluster of cases was suspected to have an occupational cause and led to the recognition of chronic beryllium disease for the first time. Beryllium has not been used in fluorescent light bulb manufacture since 1949.

4. How do cases of beryllium disease present?

The cardinal symptoms of clinical beryllium disease are chronic cough and exertional shortness of breath. In addition, patients may have wheezing, fevers, weight loss, and profound fatigue. Workforce screening programs may identify asymptomatic workers as well. The most

sensitive clinical test for abnormality is oxygen desaturation on exercise tolerance testing, which often long precedes abnormal pulmonary function tests (obstructive or restrictive), low diffusing capacity, interstitial changes on chest radiograph, or hilar adenopathy (in a minority of cases).

5. Why are only a small percentage of beryllium-exposed workers affected?

Beryllium disease arises only in workers who develop a cell-mediated immune response to beryllium. This T-helper cell response can be measured with the beryllium lymphocyte proliferation test, using mononuclear cells from peripheral blood or bronchoalveolar lavage. The sensitivity of the blood test varies from laboratory to laboratory and may be only 50%. In contrast, lavage cells nearly always respond to beryllium, although alveolar macrophages in smokers may inhibit the lymphocyte response and may need to be removed from the assay.

6. Describe the diagnostic criteria for beryllium disease.

The diagnosis of beryllium disease requires evidence of lymphocyte proliferation to beryllium in blood or lavage lymphocytes. This specific characteristic differentiates the disease from other granulomatous diseases, such as sarcoidosis and hypersensitivity pneumonitis. The diagnosis usually requires bronchoscopy for bronchoalveolar lavage and transbronchial lung biopsy in asymptomatic cases detected in screening programs. In clinically evident disease, a chest radiograph compatible with granulomatous disease may make tissue evidence of granulomas unnecessary in the setting of beryllium sensitivity.

7. Which screening tests are appropriate for beryllium-exposed workers?

Early diagnosis of beryllium sensitivity is now possible with the beryllium lymphocyte proliferation test on screening blood samples. Workers with abnormal blood tests may have sensitization only or subclinical beryllium disease, a diagnosis made on bronchoscopy. A small percentage of cases with abnormal lavage lymphocyte proliferation tests have normal blood tests; these cases can be identified with chest radiograph screening. Pulmonary function tests, diffusing capacity, and symptom questionnaires are too insensitive and nonspecific to be useful except in the extraction industry.

8. How do you judge whether a worker has had significant beryllium exposure?

Any beryllium exposure is significant. In nearly every plant studied, both historically and recently, cases of beryllium disease have occurred among persons without industrial job descriptions, including secretaries, accountants, security guards, and inspectors of final product. Thus, the physician evaluating a patient with granulomatous disease should inquire about the industry as well as the job description. Cases have occurred among workers in former beryllium plants who were hired long after beryllium production ceased. Similarly, cases have occurred among family members of beryllium workers and community residents living in proximity to beryllium plants.

9. Since idiosyncratic cases occur with brief or minimal exposures, what is the basis of the permissible exposure limits?

The permissible exposure limits of 2 $\mu g/m^3$ for a time-weighted average, 5 $\mu g/m^3$ for a short-term exposure limit, and 25 $\mu g/m^3$ as a ceiling exposure limit were not based on empiric data. The standard is known as the "taxicab standard" because it was proposed on the basis of a conversation between experts in a cab who believed that the standard should be analogous to other toxic metals (proportional to atomic weight). Nevertheless, the occurrence of "chemical pneumonitis" in beryllium workers was thought to be eliminated by adherence to the taxicab standard. The incidence of chronic irreversible disease may not have changed with these standards. Nevertheless, cross-sectional studies of modern beryllium-exposed populations have uniformly found process-related risks, suggesting that exposure characteristics are critical to disease risk. In one plant with usable historical measurements, the machining jobs had highest risk and highest median exposures. In another plant, however, the process with the highest contemporary risk did

not have the highest indices of gravimetric exposure. Reexamination of permissible exposure limits may take into account respirable beryllium exposures (or other characteristics apart from total mass of beryllium) that characterize high-risk processes.

10. Can susceptibility to disease be identified?

Approximately 80% of cases of beryllium disease are associated with a genetic marker, HLA-DP glu69, which is present in 30–40% of the general population as a normal variant. Accordingly, its predictive value for beryllium disease is very low. Even if it were to be used in preplacement evaluation (an ethically dubious practice), beryllium disease occurs among workers without the marker. Research continues on this and other markers with the hope that understanding of the molecular mechanism of beryllium disease may lead to secondary prevention.

The lymphocyte proliferation test is not a test of susceptibility to beryllium disease, although it identifies a postexposure group with the immunologic response necessary for disease, most of whom already have granulomatous disease. The remainder are at high risk of developing granulomatous disease.

11. Is there a role for determining beryllium concentrations in tissue, blood, or urine?

No relation has been shown between lung or urine concentrations of beryllium and risk or severity of disease. This finding may be predictable for a disease now known to be immunologically mediated. Beryllium remains in tissue and urine for decades after exposure to insoluble beryllium compounds, such as beryllium oxide in ceramics and metal industries. The only use of beryllium assays in biologic samples is in research. For example, demonstration of beryllium in lung granulomas by laser microprobe mass spectroscopy is of interest in current documentation of beryllium disease in a household contact of a beryllium worker. The presence of lymphocyte proliferation to beryllium indicates prior exposure, whether or not beryllium can be measured in biologic materials.

12. How should you pursue the diagnosis of beryllium disease in persons with known granulomatous lung disease?

Beryllium disease cannot be distinguished on pathologic grounds from sarcoidosis, hence the term "Salem sarcoid." The only way to ensure that a case of sarcoidosis is not due to beryllium is to test blood and lavage lymphocytes with the beryllium lymphocyte proliferation test. Bystander, household, and community cases make it difficult to rule out beryllium disease with personal work history alone. On the other hand, sarcoidosis does occur in beryllium workers.

13. Is beryllium disease curable?

The acute pneumonitis recognized in the 1940s was cured by exposure cessation if the patient survived the acute illness. In contrast, chronic beryllium disease is not usually improved by exposure cessation and indeed may develop decades after exposure has ceased. Although not curable, the disease is responsive to corticosteroids in most cases, particularly if the diagnosis is made before fibrosis is a dominant characteristic. Unfortunately, most patients with physiologic impairment require lifelong steroids for disease suppression. In asymptomatic cases identified in workplace screening programs, steroids are not commonly used until clinically indicated by objective deterioration.

14. A 26-year-old construction worker applies for a position in a beryllia ceramics plant as a plant facilities worker. On preplacement testing, he is found to have an abnormal beryllium lymphocyte proliferation test, a normal chest radiograph, normal pulmonary functions, and no chest symptoms. The plant physician learns that he was involved in demolition work at the Rocky Flats nuclear weapons plant after production ceased. What would you recommend for job placement and worker notification?

The applicant's abnormal lymphocyte proliferation test indicates that he is sensitized to beryllium as a result of prior exposure. In this case, the exposure was likely to have been in the

former nuclear weapons plant. Most industrial facilities with beryllium production remain contaminated despite clean-up efforts. In demolition work, settled dust in ventilation systems or on false ceilings leads to predictable but often unrecognized exposure. Although the applicant has no symptoms or signs of beryllium disease, he has not undergone bronchoscopy to rule out the diagnosis of granulomatous lung disease. With or without lung disease, it is medically prudent to restrict him from further beryllium exposure. In addition, he should be notified of the screening test result. He may want to consult his previous employer at Rocky Flats to participate in a worker surveillance program sponsored by the U.S. Department of Energy for former nuclear weapons workers. At a minimum, the applicant needs to bring his previous beryllium exposure and sensitization status to the attention of his physician if he develops chest symptoms.

CONTROVERSIES

15. Does beryllium cause cancer?

Beryllium causes lung cancer in several animal species. In addition, a small excess of lung cancer has been documented in an industry-wide cohort of beryllium workers and among persons with beryllium disease in the U.S. Beryllium Case Registry. On this basis, the International Agency for Research on Cancer designated beryllium as a probable human carcinogen. The beryllium industry disputes this designation, saying that the excess in lung cancer arose in only one or two plants among seven.

16. Is workplace screening warranted?

Although beryllium lymphocyte proliferation testing can identify sensitized persons, most of whom have beryllium disease in an asymptomatic stage, no investigators have studied whether early diagnosis changes prognosis, either by early treatment or by removal from beryllium exposure. Only in the beryllium extraction industry does evidence indicate that removal of symptomatic workers can lead to resolution or improvement of symptoms. In the absence of data in the rest of the industry, some beryllium plants do not remove workers with sensitization or subclinical disease from beryllium exposure, although it seems prudent to do so from a medical point of view.

Because efficacy of screening in changing prognosis has not been studied, the rationale for screening is the identification of risk factors in the worker population that may lead to preventive measures. In contemporary screening, process-related risk factors have been demonstrated in every plant studied. These work factors can form the basis for preventing disease in the future and for understanding the qualitative and quantitative exposures that confer risk of beryllium disease. Screening is justified for surveillance, but the benefit for individual workers remains unclear.

17. Was acute beryllium disease a toxic pneumonitis?

Acute beryllium disease was not recognized in the United States after 1953, although exposures in excess of the standard have occurred in many plants. Has the disease really disappeared, or is it no longer diagnosed, even in the extraction industry where it occurred historically? In reviewing the clinical descriptions of the disease from the 1940s, including pathologic reports for fatal cases, acute disease was accompanied by mononuclear cell alveolitis and interstitial infiltrate similar to what is seen in chronic disease. The radiographic abnormality lagged about 3 weeks after symptomatic presentation. Such features suggest that it was not a toxic pneumonitis with acute pulmonary edema as seen in phosgene poisoning. Symptomatic disease often recurred in workers who returned to beryllium work after resolution of acute pneumonitis. In light of current understanding of the cell-mediated immunologic nature of chronic beryllium disease, acute disease seems to be remarkably similar.

On the other hand, acute disease was clearly reversible with restriction from exposure, whereas the chronic disease recognized today is not. The time course of improvement of the acute disease was months. The explanation may lie in the biopersistence of different beryllium compounds. The acute disease arose in the setting of exposure to soluble salts. Persons sensitized to beryllium with such exposure are likely to improve as they clear the antigen over time. In

contrast, beryllium metal or oxide is an insoluble antigen that may result in sensitization even years after workplace exposure has ceased. Once the worker is sensitized, the granulomatous reaction persists along with the antigen. Perhaps for this reason two distinct clinical courses of disease were described historically in different sectors of the industry. The possible identity of pathologic mechanism may explain why a high proportion of patients with acute beryllium disease eventually progressed to chronic beryllium disease in industrial sectors with exposure to both soluble and insoluble beryllium compounds.

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