Chapter 25

BERYLLIUM

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INTRODUCTION

Beryllium is a naturally occurring element found on the earth's surface in rocks at concentrations of 1 to 15 mg/kg. In the periodic table, beryllium appears in group IIA, alkaline earth elements. It has an atomic weight of 9.012, with two common oxidation states, Be(0) and Be(+2).[1] It has a melting point of 1,287°C and a boiling point that ranges from 2,469° to 2,970°C.[2] Beryllium is not naturally found as a free metal because of its high reactivity. The important beryllium minerals in the world are beryl ($Be_3Al_2(SiO_3)_6$) and bertrandite ($Be_4Si_2O_7(OH)_2$).[3,4] Beryllium is a light-weight, grey metal that is relatively transparent to x-rays and has nonmagnetic properties, along with low density, high tensile strength, and good corrosion resistance.[3,4] It is widely used in manufactured products, ranging from nuclear weapons to golf clubs and helicopter rotor and airplane parts, due to its light weight and high tensile strength. Beryllium has chemical properties like aluminum, but is only two-thirds the weight of aluminum, and it has six times the tensile strength of steel.[5,6]

The chemical and physical properties of beryllium make it important for military applications, including nuclear bomb casings, non-sparking tools for the ammunition industry, and aircraft applications in helicopters and airplanes. At the same time, beryllium's unique properties make it potentially extremely toxic for people who come in contact with either its metal or alloy form.[7]

This chapter will discuss in detail the production and industrial uses of beryllium, with a focus on how beryllium is used in military applications. The environmental and occupational sources of exposure will be highlighted. The chapter will review the health effects of beryllium exposure and the supporting medical evidence, including sensitization, chronic beryllium lung disease, genotoxicity, and lung cancer. The legal and regulatory requirements, as well as exposure prevention and treatment strategies, will be outlined. Beryllium's toxicological properties will be examined, with a focus on pulmonary and renal changes. The basis for the genetic predisposition for beryllium-exposed workers to develop sensitization and chronic beryllium lung disease will be explored.

Additionally, the chapter will discuss elements of a medical surveillance program for beryllium, including a review of available biomarkers of exposure and effect, such as the beryllium lymphocyte proliferation test (BeLPT). However, medical surveillance for beryllium exposure is complicated because x-ray changes do not always appear right away, and pulmonary function tests do not change rapidly in response to exposure. New studies report improved sensitivity and specificity for the BeLPT, which requires that split samples be drawn for confirmatory testing at one or more laboratories.

INDUSTRIAL USE

The United States is one of only three countries that produce beryllium products. It is the leading manufacturer of beryllium metals, alloys, and oxides.[8] US production of beryllium was reported as 180, 235, 200, 216, and 270 metric tons in 2010, 2011, 2012, 2013, 2014, respectively.[8] Beryllium-copper-nickel alloy was first used in the United States in 1926 in the manufacture of fluorescent lighting. In the 1940s, a small cluster of chronic beryllium disease (CBD) was identified in fluorescent lighting plant workers.[9]

The US Geological Survey estimated that consumer electronics uses 42% of the available beryllium, telecommunications uses 11%, the Department of Defense uses 11%, commercial aerospace and energy applications both use 8%, and the remailing 28% is used in appliances, automotive electronics, and medical devices.[8] The three primary beryllium-containing materials used today in the electronics, aerospace, defense, and automotive industries are beryllium metal; beryllium alloys including copper, aluminum, magnesium, or nickel; and beryllium oxide. Beryllium is found in the vital sensing equipment of fire suppression systems and automobile airbags. Its use in automobile ignition control systems improves gas mileage and decreases emissions. Additionally, it is critical to the functioning of such medical equipment as laser bores, mammography x-ray windows, and pacemakers. Because of its magnetic transparency, strength, and corrosion resistance, beryllium is utilized in satellites, weather forecasting equipment, and aircraft landing gear bearings. Beryllium's light weight and conductivity make it ideal for use in mobile phones and computer systems. Compounds and alloys containing 40% to 100% beryllium are used in the defense industry in targeting systems, lasers, high-speed circuitry, missile production, radar systems, and infrared countermeasure equipment.[9] In the nuclear industry, beryllium is used to absorb and reflect neutrons and to produce neutron sources.[10] Exhibit 25-1 lists jobs with potential exposure to beryllium, and Exhibit 25-2 lists manufactured products that include beryllium.

ENVIRONMENTAL EXPOSURE

Beryllium is naturally occurring in rocks, coal, oil, soil, and volcanic dust, and it is taken up by plants. The average US soil concentration of beryllium is 0.6 mg/kg[3]. Beryllium will dissolve in water and can be toxic to fish at high levels.[11] Exposure to beryllium in the general population varies by geographic location; drinking water concentrations average 190 ng/L but range from 10 to 1,220 ng/L.[12] The Geological Survey's National Water-Quality Assessment Program, a comprehensive study of trace elements detected in groundwater across the United States from 1992 to 2003, collected data from 5,183 monitoring and drinking-water wells and found that beryllium levels did not exceed 4 μg/L.[13]

The average US air concentration of beryllium is 0.3×10^{-4} μg/m^3; however, in metropolitan areas, the concentration is markedly higher, with a mean of 0.2×10^{-3} μg/m^3.[14] Atmospheric beryllium comes from three primary sources: anthropogenic sources account for 45.3% of atmospheric beryllium, windblown dust accounts for 52%, and volcanic activity accounts for 2%.[14] Inhalation of beryllium-containing fumes and dust originating from processing plants poses the most serious hazard to people.[11] In 2008, eight CBD cases were diagnosed in the community surrounding a beryllium manufacturing plant in Reading, Pennsylvania.[15] Between 1974 and 2010, environmental air sampling was conducted at the Lawrence Livermore National Laboratory in California, where beryllium is manufactured, machined, and stored. The beryllium airborne concentrations at the sites ranged from 0.2 to 490 pg/m^3, with a median concentration of 11.8 pg/m^3.[16] Monthly sampling showed seasonal variation in beryllium levels, with the highest levels in late summer/early fall, when temperatures and wind speed are elevated and precipitation is low. Lower levels of beryllium were observed in the winter months, when precipitation is higher.[16]

Among individuals who are not employed in the beryllium industry, exposure occurs primarily through smoking, food, and water. While the nonoccupational intake of beryllium is unknown, estimates have ranged

EXHIBIT 25-1

WORKERS WITH POTENTIAL OCCUPATIONAL EXPOSURE TO BERYLLIUM

- Primary beryllium production workers
- Workers processing beryllium metal/alloys/composites
  - foundry workers
  - furnace tenders
  - machine operators
  - machinists
  - metal fabricators
  - welders
  - dental technicians
- Secondary smelting/refining (recycling electronics, metals)
- Abrasive blasters (slags)*

*Certain types of slags (coal, copper) used in abrasive blasting operations may contain trace amounts of beryllium (< 0.1 % by weight). Due to high dust conditions in abrasive blasting, workers may be exposed to dangerous levels of beryllium.
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EXHIBIT 25-2

MANUFACTURED PRODUCTS THAT USE BERYLLIUM

- Aerospace (aircraft braking systems, engines, satellites, space telescopes)
- Automotive (antilock brake systems, ignitions)
- Ceramic manufacturing (rocket covers, semiconductor chips)
- Defense (components for nuclear weapons, missile parts, guidance systems, optical systems)
- Dental labs (alloys in crowns, bridges, and dental plates)
- Electronics (x- rays, computer parts, telecommunication parts, automotive parts)
- Energy (microwave devices, relays)
- Medicine (laser devices, electro-medical devices, x-ray windows)
- Nuclear energy (heat shields, reactors)
- Sporting goods (golf clubs, bicycles)
- Telecommunications (optical systems, wireless base stations)

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from 0.12 to 100 μg/day.[12] The average whole-body burden of beryllium in individuals who are not occupationally exposed is less than 0.08 mg/kg, although it is slightly higher in lung tissue, which averages 0.20 mg/kg.[17] A smoker who smokes 20 cigarettes per day is exposed to 1.5 μg of beryllium per day.[18]

OCCUPATIONAL EXPOSURE

In 1943, Dr Van Ordstrand of the Cleveland Clinic published the first reported cases of beryllium-related disease in workers at two beryllium production plants in Cleveland.[19] In 1946, when doctors Irving Tabershaw and Harriet Hardy attributed previously diagnosed sarcoidosis cases to exposure to beryllium, the notion of beryllium-related lung disease began to gain acceptance.[20] These findings raised concern about the health of the general public and for workers in the lighting industry. As a result, use of phosphors of beryllium was discontinued in the manufacture of fluorescent lights after 1949.[9]

The utilization of beryllium in the atomic weapons industry has decreased over the last 4 decades due to the worldwide downsizing of nuclear arsenals. However, beryllium is now used in a variety of other industries. Prior to 2000, CBD was reported to affect between 2% and 6% of exposed workers, with rates as high as 16% for those in beryllium manufacturing and maintenance jobs. With aggressive exposure controls in modern worksites, the prevalence of beryllium sensitization (discussed below) was decreased from 18% to 1% in one company's plant over 24 months.[21]

The total number of workers with beryllium exposure has been as high as 800,000, but the numbers have declined over the last 2 decades. In 2004, the estimated total of federal and private beryllium workers was 134,000.[21,22] The Occupational Safety and Health Administration (OSHA) estimates that in 2017, approximately 62,000 workers were potentially being exposed to beryllium in approximately 7,300 establishments in the United States. [23,24] In addition, family members of beryllium workers also have potential exposure from contaminated work clothing and vehicles. Presently, beryllium workers in primary beryllium manufacturing and alloy production, and workers in recycling, have the highest average exposures to beryllium.[23,24]

The number of workers in the Department of Defense exposed to beryllium remains steady. Exposures to Air Force personnel mostly occur during installation and repair of aircraft systems that include bushings, bearings, and washers made of beryllium copper alloy, as well as braking systems on the Lockheed C-5 Galaxy built before 1980. Aircraft panel removal generates dust from the wear of alloy materials. Forward-looking infrared systems, low-altitude navigation-targeting infrared for nighttime operations, and field instruments for detecting low-energy radiation all contain beryllium. Service of equipment by maintenance personnel has the potential to expose workers to 61 different work processes that pose a likely inhalational hazard.

The National Academy of Sciences Committee on Toxicology reviewed Air Force personnel exposures to beryllium and recommended several steps the Air Force should take to protect its personnel. First, skin and respiratory exposures should be minimized by maintaining effective controls for processes that generate dust and fumes. Next, the committee recommended screening personnel and putting the resulting information into a centralized surveillance database. Further, the Air Force should do a comprehensive exposure assessment by characterizing each job task and identifying the beryllium in all materials in the workplace, then remove products containing beryllium as soon as feasible. Lastly, the Air Force should train personnel on the health hazards of beryllium and steps necessary to prevent exposure.[25]

The Navy has discontinued the use of beryllium in fabricating dental prosthetics for patients. However, beryllium continues to be used in commercial dental bridges and prosthetics and fabrication facilities. Significant numbers of Army workers and contractors are exposed to beryllium in the maintenance shops at ammunition plants around the country where nonsparking tools are necessary to prevent explosion. The grinding and reconditioning of these tools puts maintenance workers and others in the immediate vicinity at risk of exposure. Further, rotary-wing aircraft mechanics are routinely exposed when maintenance work for Army and Navy helicopters is performed on the main and tail rotor assemblies, which contain beryllium in component parts.

Known occupational risk factors include work in ceramics production, machining of various types of beryllium, beryllium metal production, copper-beryllium alloy melting and casting, processing of alloy rod and wire products, and work in analytic laboratories.[26] Workers at highest risk for developing CBD are those who work in industries that generate airborne beryllium particles, and those involved in machining beryllium usually have the highest levels of exposure among beryllium workers. This group is at an increased risk of becoming sensitized to beryllium and developing CBD.[26] Machining, either by grinding, deburring, lathing, milling, or other processes, produces beryllium particles that are highly respirable and easily

deposited in the alveoli. When beryllium is machined, 50% of the particles generated are larger than 0.6 μm in diameter. The remaining 50%, which are smaller than 0.6 μm, tend to be dispersed throughout the work area, exposing others not involved in the machining process to beryllium and CBD risk.[27]

At the Lawrence Livermore site, beryllium was found in the carpets after vacuuming, at a concentration ranging from 0.002 to 0.480 μg/cm^2. Beryllium was also detected in surface dust at the front offices and wire annealing areas of a copper-beryllium alloy facility at Lawrence Livermore at concentrations of 0.05 to 13.6 μg/cm^2. At an industrial facility located in Schenectady, New York, beryllium concentrations in overhead dust were reported to range from 19.4 to 151 μg/cm^2.[16]

REGULATION AND LEGISLATION

The first steps toward the establishment of an occupational exposure limit (OEL) for workers came in 1947 when the Atomic Energy Commission's Health and Safety Laboratory, under the direction of Merrill Eisenbud, began to investigate the health impacts of beryllium exposure.[28,29] Based on this work, a permissible maximum peak exposure limit of 26 μg/m^3 over a period of 30 minutes was recommended for workers in the beryllium industry. A community ambient air standard of 0.01 μg/m^3 averaged over a 1-month time interval was also proposed to protect the public living near beryllium manufacturing facilities.[22] The establishment of this recommended ambient air standard was driven by a cluster of CBD cases in nonoccupationally exposed individuals within a 0.75-mile radius of a beryllium plant in Lorain, Ohio. In 1948 the average beryllium concentration in the air within 0.25 miles of this plant was 1 μg /m^3, 100 times the proposed standard.[30]

Eisenbud proposed an 8-hour time-weighted average (TWA) of 2.0 μg/m^3 as the OEL, based on the known toxicity of other heavy metals and their atomic weights,[31] which was implemented by the Atomic Energy Commission in 1949.[22] The OEL of 2.0 μg/m^3 was subsequently adopted by the American Industrial Hygiene Association in 1956, and by the American Conference of Governmental Industrial Hygienists in 1959 as a threshold limit value (TLV). The American National Standards Institute (ANSI) incorporated this value as a consensus standard in 1970, and in 1972 OSHA adopted the ANSI standard as the permissible exposure limit (PEL).[22]

In January 2017, OSHA published a new beryllium final rule that lowered the PEL for beryllium to 0.2 μg/m^3 of air, averaged over 8 hours. OSHA also lowered the short-term exposure limit for beryllium to 2.0 μg/m^3 of air over a 15-minute sampling period.[23,24] This rule provides staggered compliance dates to give employers time to meet the requirements and ensure the needed protections are put in place. One year after the effective date of the rule, most provisions must be adopted. Employers must put change rooms and showers in place 2 years after the rule was published, and they must install engineering controls no later than 3 years after the rule was published.[23,24]

The rule also requires employers to limit access to areas with high levels of beryllium and provide respiratory and dermal protection in the form of personal protective clothing to workers who must enter these areas. They must also develop a written exposure control plan and train workers on the plan. Lastly, employers are required to offer workers medical surveillance when their exposure exceeds the action level for beryllium (discussed below).[23,24]

HEALTH EFFECTS

The most common health effects associated with overexposure to beryllium in the workplace include acute beryllium disease (ABD), beryllium sensitization, CBD, and lung cancer.[23,24]

Pathophysiology of Chronic Beryllium Disease

CBD is an immune-related disease. This categorization is based on observations of CBD in individuals exposed to low airborne concentrations of beryllium. Further, the tissue burden of beryllium did not correspond to the severity of the disease. In addition, several cases of CBD were known to occur months to years after the termination of exposure. Finally, beryllium causes a delayed skin test response as well as a granulomatous response in the lungs and skin.[32]

A mechanism has been proposed for the development of lung inflammation and granuloma formation in CBD, which occurs during and after beryllium exposure.[33] Beryllium particles, acting as haptens, bind to proteins in lung tissue. The protein-bound beryllium particles are ingested by alveolar macrophages, which act as antigen-presenting cells to CD4$^+$ T lymphocytes. Beryllium alone also causes activation of T cells. T lymphocytes proliferate in response and, combined with macrophages, release inflammatory cytokines

(IFN-γ, TNF-α, IL-2, and IL-6) that promote the accumulation, activation, and aggregation of macrophages, resulting in the development of granulomatous inflammation through a cell-mediated, type IV mechanism. Beryllium also induces macrophage apoptosis, which reduces clearance from the lung, causing continual reexposure.[34–36]

Acute Beryllium Disease

ABD is a rapid onset form of chemical pneumonia that results from breathing high airborne concentrations of beryllium.[23,24] ABD is generally associated with exposure to beryllium levels at or above 100 $\mu g/m^3$ and may be fatal in 10% of cases. ABD is extremely rare in the workplace today due to more stringent exposure controls implemented following occupational and environmental standards set in the 1970s.[23,24]

In 1997 two cases of ABD were detected in workers exposed to beryllium fluoride in a metal production department that was part of a reduction furnace operation in Korea.[37] Exposure levels to beryllium were low, with most of the facility's air concentrations under 10 $\mu g/m^3$. After working for several months, the workers complained of shortness of breath, chest pain, and a dry cough. Chest x-rays were normal, but pulmonary function tests showed decreases in forced vital capacity and carbon monoxide diffusing capacity. With continued exposure, the respiratory symptoms worsened, as did both pulmonary function tests, but the chest radiographs remained unchanged. After removal from exposure, the respiratory symptoms and pulmonary function test results were improved. One of the workers returned to working with soluble beryllium, and his respiratory symptoms returned; he had impaired lung function within several months. The second worker went to work in another area of the facility, which involved less exposure to beryllium compounds. Eighteen months later, both workers were asymptomatic, but chest radiographs and biopsies revealed non-caseating granulomas. Because of these cases, it was hypothesized that ABD may be part of the continuum from acute to chronic beryllium disease, and that ABD was likely due to an immunological response to beryllium rather than an irritant response.[37]

Beryllium Sensitization

Beryllium sensitization is the activation of the body's immune response to beryllium. Beryllium sensitization can result from inhalation or skin exposure to beryllium dust, fume, mist, or solutions.[38,39] Two positive BeLPT tests over any time period define sensitization.[40,41] While no clinical symptoms are associated with sensitization, a sensitized worker is at risk of developing CBD when inhalation exposure to beryllium has occurred.[42–44]

Several studies have evaluated the prevalence of beryllium sensitization among workers at different types of facilities, but most of the studies lacked exposure monitoring data. The prevalence of beryllium sensitization in workers has varied from a low of 1.3% in a nuclear weapons facility to a high of 7% to 19% in a beryllium production facility.[45–47]

Symptoms and Effects of Chronic Beryllium Disease

CBD is a chronic granulomatous lung disease caused by inhaling airborne beryllium after becoming sensitized to beryllium. The currently accepted diagnostic criteria for CBD in patients with known exposure to beryllium are sensitization to beryllium and pulmonary epithelioid granulomas identified on lung biopsy.[48]

Common symptoms of CBD are shortness of breath, unexplained coughing, fatigue, weight loss, fever, and night sweats. CBD can result from inhalation exposure to beryllium at levels below the current OSHA PEL (0.2 $\mu g/m^3$).[23,24] Progression from sensitization to CBD can vary among individuals, and not all sensitized individuals go on to develop CBD.[49,50] After initial exposure to beryllium, some workers may quickly develop signs and severe symptoms of CBD. Others may not experience signs and symptoms until months or years after initial exposure. Symptoms can sometimes worsen even after the worker has been removed from exposure.[51–53] CBD can progress to a chronic obstructive lung disorder, resulting in loss of quality of life and the potential for decreased life expectancy. CBD shares many signs and symptoms with pulmonary sarcoidosis, a granulomatous lung disease of unknown cause or origin.[48,54]

Individuals who have been exposed to beryllium do not respond uniformly. Most people show no evidence of sensitization (immune response) or of CBD. Some individuals become sensitized but have no evidence of CBD.[51,53] Some individuals demonstrate evidence of interstitial lung disease that may or may not be characterized by microscopic granulomas, but macroscopic granulomas are usually seen on x-ray as the disease progresses.[48] It is thought that only sensitized individuals progress to develop CBD.[48] To date, it is unknown if cessation of exposure to beryllium in sensitized workers reduces the progression rate to CBD.[53]

Latency (length of time from exposure to CBD development) ranges from zero to more than 25 years.[48,53] One study followed beryllium-sensitized

workers over 5 years, with 30 of 79 workers still employed at the end of the study. During the 5-year period, 30% of the original group of 79 workers developed CBD. The rate of progression from sensitization to CBD was examined: approximately 13% of workers developed CBD at year 2, 19% had developed CBD at year 4, and 37% of workers had developed CBD by year 6.[55,56]

The study also evaluated the connection between beryllium particulate size and CBD risk. Because CBD is a granulomatous disease found primarily in the alveolar regions of the lung, it was thought that only respirable beryllium particles less than 10 μm in diameter were responsible for CBD, and this was confirmed. Another study showed that more CBD cases occur in areas when particle size is less than 5 μm in diameter, and fewer cases occur in areas where particle size is larger than 5 μm.[26] These findings support the notion that the size of respirable particles may be a good indicator of CBD risk.

In addition, beryllium can damage the liver by producing granuloma formation adjacent to or within the portal tracts. Dot necrosis, acidophilic degeneration, white blood cell infiltration, fibrosis, portal cirrhosis, and Kupffer cell proliferation have been reported.[57] Similarly, beryllium can induce granuloma formation and fibrosis in the kidney. However, renal findings are rarely noted in the absence of significant pulmonary disease. Hypercalcemia, hypercalciuria, and calcium kidney stones may occur.[58]

Carcinogenesis

Based on numerous studies in occupational settings, OSHA has determined that occupational exposure to beryllium causes lung cancer in humans. In addition, the International Agency for Research on Cancer classified beryllium as a group 1 lung carcinogen in humans in 1993, 2009, and 2015.[59] The Environmental Protection Agency and the National Toxicology Program also consider beryllium to be a carcinogen.[60,61] One large study examined lung cancer and urinary tract cancer mortality in 9,199 workers at seven beryllium facilities in the United States. Beryllium exposure was assessed by estimating maximum and daily average exposure and time spent at specific jobs to create a job-exposure matrix. The study found elevated risk of lung cancer risk of 20% and 45% at two of the facilities, an overall combined increased risk of 17% across all facilities, and a 3-fold increase risk of uterine cancer also across all facilities.[62] Another study reported a latency of 20 years for cancer associated with beryllium exposure.[62]

Dermatologic Effects

Nonpulmonary forms of CBD can present as a granulomatous disorder that affects the lymphatics and skin. Skin exposure to beryllium in sensitized individuals manifests initially as a dermatitis. Skin or pulmonary exposure (unrelated to dermatitis or beryllium implantation in the skin) may lead to subcutaneous granulomas. Implanted beryllium particles may result in skin ulceration that requires removal of the particles for resolution.[57,58]

Skin exposure to beryllium results in mild to moderate changes in the skin. Initially, spongiosis involving the lower layers of the epidermis and focal edema of the papillary epidermis were observed on skin biopsy obtained 96 hours postexposure.[63] A skin biopsy obtained 2 to 5 weeks postexposure in the same patient showed granuloma formation, with spongiosis and edema resolved.[63] Skin patch testing in individuals with CBD have resulted in strongly positive reactions that were characterized by erythema, induration, and vesicles.[64]

Biomarkers of Exposure and Effect

Blood Beryllium Levels

A 2008 study of ten subjects in Montreal, Canada, showed beryllium can be detected in the blood and serum using graphite furnace atomic absorption spectrometry. The average concentration of beryllium detected was 0.63 μg/L in the blood and 0.43 μg/L in serum. Smokers had slightly higher levels than nonsmokers.[65]

Urine Beryllium Biomarkers

A 2011 study conducted in the United Kingdom examined beryllium levels in the urine of a group of workers at an aluminum smelting facility and in a group of non-exposed individuals.[66] The mean and 90th percentiles of beryllium in the urine for workers at the aluminum smelter were 19.5 and 42.0 ng/L, respectively, while the mean and 90th percentile of the control group were 11.6 and 20.0 ng/L, respectively.[66]

Beryllium Lymphocyte Proliferation Test

The BeLPT is an immune-based test that measures the reaction of lymphocytes in body fluid, usually venous blood or broncho-alveolar lavage (BAL), to beryllium.[67] Lymphocytes previously sensitized to beryllium respond with higher rates of proliferation and radioactive thymidine uptake.[68] Although the test

is ingenious, the nuances and difficulties of cell culture and measuring thymidine uptake have made its standardization across laboratories, and even within laboratories, challenging.[69,70]

The sensitivity and specificity of the BeLPT test has improved over the past 10 years. One recent study involved over 25,000 BeLPT tests done on 12,194 workers employed at 18 Department of Energy sites. The workers were exposed to beryllium or beryllium oxide and beryllium-copper alloy. A false positive result was defined as an abnormal test result that could not be confirmed by additional BeLPT retests conducted within 2 months of the original sample. The false positive rates ranged from 0.0 to 3.4%, with an average false positive rate of 1.1%. False negative results were assessed among workers with two or more abnormal results and were defined as a normal result occurring within 2 years of the initial abnormal result. Overall, the false negative rate was 31.7%. Inter-laboratory agreement of abnormal results ranged from 26.2% to 61.8%. Test sensitivity, the probability that a patient with CBD will have an abnormal BeLPT result, was 68.3%. Test specificity, the proportion of normal tests in all patients who do not have CBD, was 96.9%.[71]

Another analysis of the BeLPT sensitivity and specificity employed different testing algorithms, one with testing performed at one lab followed by analysis at two different labs, and a second algorithm that employed split samples analyzed at two different laboratories. The second algorithm yielded the highest sensitivity and specificity for the BeLPT test, with a sensitivity of 86.0% and a specificity of 99.8%.[72]

The positive predictive value (the likelihood that a person who meets the criteria is truly sensitized to beryllium) varies with the beryllium sensitization prevalence in the population. If the prevalence in the test population is low (1%), then the positive predictive value is low at 37%. At a 10% prevalence, the positive predictive values was 99.7%.

Another test has been developed to assess beryllium sensitization using a cytokine-based assay of $CD4^+$ T cells.[73] An enzyme-linked immune spot (ELIS) analysis was performed to measure interferon (IFN-γ) gamma-secreting $CD4^+$ T cells. In former beryllium workers, similar rates of sensitization were found using BeLPT (8.1%) and an IFN-γ ELIS test (10%). Among current workers, the BeLPT identified only 1.3% of workers as sensitized, compared to 9.9% identified using the IFN-γ ELIS test. The difference in the test results was thought to be due to poor proliferation of beryllium-specific $CD4^+$ T cells. The IFN-γ ELIS test had a sensitivity of 85% and a specificity of 100%. The IFN-γ ELIS test was also able to differentiate between beryllium sensitization and CBD. More than 93% of the beryllium-sensitized subjects had less than 10 spot-forming units, and subjects with over 40 spot-forming units had an 81% probability of progressing to CBD.[73]

Whether all workers with a positive BeLPT or IFN-γ ELIS should undergo bronchoscopy and lung biopsy is questionable. Induced sputum cytology, using a CD4 to CD8 ratio of greater than 2.5 as a cut-off, has been shown to compare with bronchoscopy and biopsy in diagnosing CBD when each are combined with a positive BeLPT.[74] However, sputum cytology has yet to become a widely accepted alternative to bronchoscopy and biopsy. OSHA regulations now permit the employee to decide whether to take advantage of medical removal based on a positive BeLPT or IFN-γ ELIS sensitization test result.[23,24]

OCCUPATIONAL SURVEILLANCE

The purpose of medical surveillance is to educate workers about potential health effects, detect early signs and symptoms of disease to eliminate ongoing exposures, and prevent short- and long-term adverse health effects. Medical surveillance programs can contribute to the success of workplace health and safety programs by identifying potential problem areas and verifying the effectiveness of existing control and prevention programs.

The beryllium standard (29 CFR 1910.1024) requires employers to offer medical surveillance to workers who are exposed above the action level of 0.1 $\mu g/m^3$ for 30 days in a year, when workers show signs or symptoms of CBD, and when workers are exposed to beryllium in an emergency or their physician or other licensed healthcare professional (PLHCP) recommends continued surveillance.[23,24] Employees may opt out of the medical surveillance program if they so choose.

The medical surveillance requirements for beryllium-exposed workers include obtaining a medical and work history with emphasis on past and present airborne exposure to or dermal contact with beryllium.[23,24] The PLHCP must also ascertain if there is a history of smoking or any respiratory conditions. The provider must examine the lungs for difficulties breathing and examine the skin for rashes.[23,24] A pulmonary function test and BeLPT are required, and the PLHCP may order other tests such as a high-resolution computed tomography (CT) scan when they feel it is necessary for the diagnostic work-up.[23,24]

The employer must provide the PLHCP with a copy of the OSHA beryllium standard, the job description that details the employee's duties involving airborne and dermal exposure potential, and available air

sampling data that shows actual beryllium exposure levels.[23,24] The employer must also give the PLHCP a description of personal protective equipment used by the employee and any abnormal results from prior physical examinations.[23,24]

The PLHCP must provide the employee with a written medical opinion that details the results of the medical examination and listing any condition that puts the employee at increased risk of injury from exposure to beryllium, as well as any newly developed medical conditions that require further evaluation or treatment.[23,24] The PLHCP must advise both the employee and employer regarding recommendations for use of personal protective equipment, and they must say whether the employee was referred to a CBD diagnostic center and whether medical removal is recommended. The PLHCP must notify the employer in writing of the date of the examination, and certify that the results of the exam were explained to the worker and that the exam met the requirements of the beryllium standard.[23,24]

GENETIC PREDISPOSITION

Genetic susceptibility contributes to the development of beryllium sensitization and progression of sensitization to CBD.[75] CBD is characterized by an accumulation of beryllium-specific $CD4^-$ T-cells in the lung. In 1993, researchers studying genetic markers noted that alleles of the major histocompatibility complex class II gene HLA-DPB1 glutamate 69 (Glu69) appears to increase the probability of CBD developing in exposed people.[76,77] The marker has been found to be expressed in 84% to 97% of CBD cases.[78] A further study found HLA-DRPhe47 to be associated with beryllium sensitization in Glu69-negative subjects.[79] An 8-fold increased rate of CBD has been demonstrated in workers who have the Glu69 marker and are exposed to elevated levels of beryllium in the workplace.[80,81]

Genetic screening holds promise for identifying individuals who have an increased susceptibility for development of beryllium sensitization or CBD. However, because of the low prevalence of beryllium sensitization and CBD in the exposed population and the limited understanding of the genetic role in beryllium-induced pathology, these markers are not useful as clinical screening tools for beryllium-related disease.[20] Further, genetic testing in the worker population has been prohibited by the Genetic Information Nondiscrimination Act of 2008.[82]

DIAGNOSIS AND TREATMENT OF CHRONIC BERYLLIUM DISEASE

Diagnosis

Beryllium disease may mimic sarcoidosis. Individuals with CBD usually present with the slow onset of exertional dyspnea, decreased exercise tolerance, fatigue, and a nonproductive cough.[35]

Criteria for diagnosing CBD include the following: (1) evidence of beryllium exposure; (2) evidence of an immune response to beryllium (ie, positive responses in blood or BAL fluid beryllium lymphocyte proliferation tests); and (3) histopathological (biopsy) evidence consistent with CBD.[25] With more advanced disease, the patient may experience progressive declines in lung volumes and diffusing capacity, eventually resulting in pulmonary fibrosis, respiratory failure, and cor pulmonale.[35] Further, the patient will exhibit anorexia, weight loss, cough, chest pain, or arthralgias. Physical exam findings may be absent except in advanced disease, when rales, tachycardia, fever, cyanosis, edema, and clubbing of fingers may be present.[52] Patients suspected of having CBD should be offered medical removal from further beryllium exposure.

Radiographic findings are those of a pneumoconiosis. They include ill-defined nodular pulmonary opacities and, with advanced parenchymal changes, hilar adenopathy may be present (though this is less common than in sarcoidosis patients). The nodular opacities are more commonly seen in the apical regions and may coalesce into large masses. A high-resolution CT scan is more sensitive in detecting granulomatous disease in its early stages. CT evaluation generally reveals small parenchymal nodules (57%) along with interlobular septal thickening (50%). Ground glass opacities (32%) and bronchial wall thickening (46%) are also common.[83]

Pulmonary function test results may be normal in the early stages of clinical disease but deteriorate with the increase in granuloma formation. The later stages of CBD may demonstrate either a restrictive or obstructive pattern, but in most cases the pattern is mixed. With advanced disease the diffusion capacity of the lung for carbon monoxide is reduced due to pulmonary epithelial damage.[51] KL-6, a known marker of epithelial cell injury, is elevated in both the serum and BAL fluid of CBD patients and has been proposed as a means of quantifying the severity of disease.[67]

Treatment

Patients suspected of having CBD should immediately be removed from beryllium exposure because improvement in lung function has been seen after

cessation of beryllium exposure. A trial of corticosteroids should be initiated as soon as possible unless contraindicated for health reasons.[84] The response to corticosteroid therapy, as measured by forced vital capacity and diffusing capacity, is short-lived but significant.[85] One study showed early treatment with steroids led to significant improvement in pulmonary function initially, but pulmonary function subsequently declined.[85] Another study noted sustained improvement in lung function following long-term corticosteroid treatment.[86] It should be noted that once pulmonary fibrosis has developed, steroid therapy will not reverse the damage.[86] Individuals started on corticosteroid therapy should be followed by regular chest radiographs and pulmonary function testing to monitor the clinical response and guide adjustments in the dose and duration of treatment.[85]

Chelating agents may prove useful in reducing the beryllium burden in exposed workers. Several chelating agents, including glutathione, 2,3-dimercapto propane sulfonic acid with sodium selenite, and D-penicillamine, were successfully used to reduce beryllium levels in the liver, kidneys, lungs, and uterus of rats.[87] D-penicillamine was the most effective chelating agent. However, more work will be necessary before the Food and Drug Administration can approve the use of these chelating agents.[87]

PREVENTION AND CONTROL

The goals of a prevention program are to limit inhalation and dermal exposures and reduce the number of employees who are directly exposed. This may be achieved by elimination or substitution of beryllium, engineering controls such as local exhaust ventilation, use of personal protective equipment, and administrative changes such as exclusion of workers from specific areas to prevent contact with beryllium.[48] The nonoccupationally exposed population encounters beryllium in food, drinking water, and the ambient air daily. There have been cases of CBD due to this type of exposure. Routine use of beryllium-containing consumer products does not pose an exposure risk because most consumer product applications do not generate particulate matter by remaining intact during normal use; performing maintenance on these products would increase the likelihood of exposure.[88]

SUMMARY

Beryllium, though extremely useful in industry, poses a threat to those involved in its manufacture and processing. Some workers exposed to beryllium develop sensitivity to it, which may lead to CBD, a disabling, irreversible pulmonary disease. There is evidence that those who have had significant exposure to beryllium may be at increased risk for respiratory cancers. Current exposure limits do not appear to adequately control the health effects of beryllium on exposed workers. Biological monitoring of beryllium exposure is challenging because there is no test specific to beryllium disease that meets all the criteria for an acceptable screening test. The BeLPT is useful in the diagnosis of CBD, but this test is not mandated in routine military beryllium occupational medical surveillance. An exposure limit of 0.2 $\mu g/m^3$ has been adopted by some government and private industries, and will be proposed by a new OSHA standard.

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