# An Official American Thoracic Society Statement: Diagnosis and Management of Beryllium Sensitivity and Chronic Beryllium Disease

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This official statement of the American Thoracic Society (ATS) was approved by the ATS Board of Directors, June 2014

**Rationale:** Beryllium continues to have a wide range of industrial applications. Exposure to beryllium can lead to sensitization (BeS) and chronic beryllium disease (CBD).

**Objectives:** The purpose of this statement is to increase awareness and knowledge about beryllium exposure, BeS, and CBD.

**Methods:** Evidence was identified by a search of MEDLINE. The committee then summarized the evidence, drew conclusions, and described their approach to diagnosis and management.

**Main Results:** The beryllium lymphocyte proliferation test is the cornerstone of both medical surveillance and the diagnosis of BeS and CBD. A confirmed abnormal beryllium lymphocyte proliferation test without evidence of lung disease is diagnostic of BeS. BeS with evidence of a granulomatous inflammatory response in the lung is diagnostic of CBD. The determinants of progression from BeS to CBD are uncertain, but higher exposures and the presence of a genetic variant in the HLA-DP β chain appear to increase the risk. Periodic evaluation of affected individuals can detect disease progression (from BeS to CBD, or from mild CBD to more severe CBD). Corticosteroid therapy is typically administered when a patient with CBD exhibits evidence of significant lung function abnormality or decline.

**Conclusions:** Medical surveillance in workplaces that use beryllium-containing materials can identify individuals with BeS and at-risk groups of workers, which can help prioritize efforts to reduce inhalational and dermal exposures.

## Contents



## Overview

Many workers are exposed to beryllium throughout the world, and sensitization to the metal continues to occur. To address this problem, an international committee of experts was convened to write a statement about beryllium sensitization (BeS) and chronic beryllium disease (CBD). After thoroughly reviewing the literature, the committee summarized the relevant evidence, drew conclusions, and described their usual approach to diagnosis and management.

- The beryllium lymphocyte proliferation test (BeLPT) is used for medical surveillance and the diagnosis of BeS and CBD. A BeLPT is considered "abnormal" if two or more of the six stimulation indices exceed the normal range. A test is typically considered "borderline" if only one of the six stimulation indices exceeds the normal range.
- A diagnosis of BeS in beryllium-exposed workers undergoing medical surveillance can be based on two abnormal blood BeLPTs, one abnormal and one borderline blood BeLPT, or one abnormal bronchoalveolar lavage (BAL) BeLPT. Workers identified as having BeS are evaluated for CBD.

An Executive Summary of this document is available at http://www.atsjournals.org/doi/suppl/10.1164/rccm.201409-1722ST/suppl_file/Executive_Summary.pdf

Am J Respir Crit Care Med Vol 190, Iss 10, pp e34–e59, Nov 15, 2014

DOI: 10.1164/rccm.201409-1722ST
Internet address: www.atsjournals.org

- Pulmonary function testing (PFT) and chest imaging (either a chest radiograph or chest computed tomography scan) are typically performed on any patient whose BeLPT is diagnostic of BeS. In contrast, bronchoscopy with transbronchial biopsy is performed on a case-by-case basis. The following criteria favor performing bronchoscopy: (*1*) absence of contraindications, (*2*) evidence of pulmonary function abnormalities, (*3*) evidence of abnormalities on chest imaging, and (*4*) personal preference of the patient.
- The diagnosis of CBD is based on the demonstration of both BeS and granulomatous inflammation on lung biopsy. Depending on the clinical setting, feasibility of certain diagnostic tests, and degree of diagnostic certainty needed, probable CBD can be diagnosed based on differing combinations of diagnostic criteria, including a clinical presentation consistent with CBD, a history of beryllium exposure, evidence of BeS (e.g., abnormal BeLPT), radiographic findings, lung histology, BAL findings, and PFT abnormalities.
- Periodic evaluation (every 1–3 yr) is performed to determine if an individual with BeS has progressed to CBD. It includes a symptom review, physical examination, and PFT, followed by a chest computed tomography scan if pulmonary function has deteriorated and bronchoscopy on a case-by-case basis.
- Corticosteroid therapy is initiated when a patient with CBD exhibits significant lung function abnormality or decline. Steroid-sparing agents are considered if significant side effects occur.
- Medical surveillance in workplaces that use beryllium-containing materials can identify individuals with BeS and at-risk groups of workers, which can help prioritize the efforts to reduce inhalational and dermal exposures. The BeLPT is the cornerstone of medical surveillance. Individuals with beryllium exposure who do not have BeS at the time of initial evaluation remain at future risk and may benefit from periodic BeLPTs.

## Introduction

Beryllium is a naturally occurring element that is extracted from ores and processed into metal, oxides, alloys, and composite materials. Industrial use of beryllium, such as machining metal parts, can lead to BeS and CBD (1). The major applications of beryllium are in automotive electronics, telecommunications, computers, aerospace, and defense equipment (Table 1). One study estimated that as many as 134,000 current U.S. workers may be exposed to beryllium (2), but the number of individuals ever exposed is much greater. Beryllium exposure is not a problem limited to the United States, as cases of CBD have been reported in many other countries (3–10). Beryllium-exposed individuals may be unaware of their exposure, and physicians may be unaware of beryllium-related health effects; therefore, BeS and CBD may not be recognized.

This statement reviews current knowledge about BeS and CBD, including its diagnosis, management, and prevention.

## Methods

The chair of the committee was selected by the leadership of the American Thoracic Society based on expertise and experience. The chair invited individuals to participate in the committee on the basis of their expertise in one or more aspects of BeS and/or CBD. Prospective members of the committee were required to disclose all financial interests relevant to the subject matter of the statement. Disclosures were reviewed by the American Thoracic Society prior to appointment of the committee, and appointments were made according to American Thoracic Society policies for management of conflicts of interest. In addition, individuals with conflicts of interest related to the subject matter of the statement acknowledged those conflicts in a face-to-face meeting, stated that they would not bias their participation on the committee, and were not assigned to work on sections of the document that addressed issues related to their conflict.

Each member with primary responsibility for writing a section of the statement searched the peer-reviewed, English language medical literature using the National Library of Medicine MEDLINE database through December, 2012. Additional references were pursued that did not appear in the MEDLINE searches but were cited in the papers reviewed (Table 2). Individual articles were appraised and then a written summary was prepared. The literature searches, study selections, and appraisals were author directed. They did not conform to the standards of a systematic review. Structured discussions were used to determine the committee members' usual approach to the diagnosis and management of BeS and CBD. Variations in clinical practice were infrequent and minor; therefore, the approach described reflects the committee's collective clinical experience in occupational health programs.

The committee's work was partially supported by funds from the U.S. Department of Energy (DOE) and the National Institute for Occupational Safety and Health (NIOSH).

## Epidemiology

The first cases of beryllium-related disease were identified soon after industrial use of beryllium began in the 1930s (11–13). In the mid-1940s, reports of "beryllium poisoning" in the United States appeared (14), including cases from the fluorescent light industry that had features of sarcoidosis (15). Additional cases appeared among workers employed in other beryllium-using industries as well as among individuals living near beryllium production facilities (16–18). The Atomic Energy Commission established a beryllium case registry for both acute disease and CBD (19, 20). The acute cases were observed among workers exposed to high levels of soluble forms of beryllium; however, the distribution of the chronic disease did not follow a linear exposure–response model. The high variability of disease occurrence in different groups of workers, disease in workers with short latency, and incident disease in community residents led to the hypothesis that CBD was immunologically mediated (17).

In 1949, the Atomic Energy Commission proposed a workplace airborne exposure limit of 2 $\mu g/m^3$ averaged over an 8-hour period (21). After the implementation of this standard, reports of acute beryllium disease ceased, and the number of new cases of CBD decreased. The U.S. Occupational Safety and Health Administration adopted the 2 $\mu g/m^3$ standard in 1975 (22). However, cases of CBD continued to occur in industries with exposures at and below this level (23, 24). The current NIOSH-recommended exposure limit is 0.5 $\mu g/m^3$ (25). In 1999, the DOE adopted a CBD prevention program that included an action level of 0.2 $\mu g/m^3$ averaged over an 8-hour period to prompt efforts to lower exposure (26).

**Table 1.** Prevalence of Beryllium Sensitization and Chronic Beryllium Disease by Type of Study and Industry: U.S. Occupational Cohorts

| Industry | N[a] | BeS [*n (%)*][b] | CBD [*n (%)*][c,d] | Comments |
|---|---|---|---|---|
| Cross-sectional studies of current workers | | | | |
| Nuclear weapons facility (29) | 51 | UP: 6 (11.8) | 4 (7.8) | Med data collected 1987–1988 (est); Be operations began 1951; mean tenure = 15 yr<br>a: Study limited to production and research and development machinists only; same facility as References 31, 36, 45, and 107<br>d: 83% of patients with BeS (5/6) evaluated with bronchoscopy |
| Nuclear weapons facility (31) | 890 | UP: 18 (2.0)<br>CP: 17 (1.9) | 15 (1.7) | Med data collected 1988–1990 (est); Be operations began 1951; mean tenure: BeS = 18 yr, non-BeS = 15 yr<br>a: Stratified random sample of workers not previously tested; same facility as References 29, 36, 45, and 107<br>c: CBD included 1 subject with BeS who refused bronchoscopy but had skin wound and ventilatory abnormalities<br>d: 94% of subjects with BeS (16/17) evaluated with bronchoscopy; study also included 22 with radiographic abnormalities, 1 of whom had CBD diagnosed |
| Beryllia ceramics (32) | 136 | CP: 8 (5.9) | 6 (4.4) | Med data collected 1992; facility opened 1981; some previously worked at facility in Reference 5; mean tenure = 6 yr<br>a: Same facility as References 34, 47, and 48<br>b: 1 subject with BeS had initial normal BeLPT, confirmed 16 mo later<br>c: Subjects with CBD included 1 in whom disease was diagnosed 16 mo later (second bronchoscopy)<br>d: 100% of subjects with BeS evaluated with bronchoscopy |
| Beryllium metal, alloy, and oxide production (33) | 627 | UP: 59 (9.4)<br>CP: 43 (6.9) | 29/632 (4.6) | Med data collected 1993–94; facility opened 1953; mean tenure = 18 yr<br>a: Same facility as References 50 and 55<br>c: Subjects with CBD included 5 with disease diagnosed before survey; CBD identified through survey = 3.8% (24/627), included 3 with "probable" CBD<br>d: 80% of subjects with BeS evaluated with bronchoscopy |
| Beryllia ceramics (34) | 151 | CP: 15 (9.9) | 8 (5.3) | Med data collected 1998; facility opened 1981; some previously worked at facility in Reference 33; tenure < 1– 0 yr; max tenure at this facility = 18 yr<br>a: Same facility as References 32, 47, and 48; 77/151 were first screened in 1992 (32), none had BeS at that time<br>c: Subjects with CBD as reported included 3 with abnormal BAL BeLPT only (no granulomas); CBD excluding latter = 3.3% (5/151)<br>d: 93% of subjects with BeS (14/15) evaluated with bronchoscopy |
| Mining/extraction (35) | 75 | UP: 3 (4.0) | 1 (1.3) | Med data collected 1996–1997; facility opened 1969; some previously worked at facility in Reference 33; mean tenure: non-BeS = 15 yr, BeS = 21 yr, CBD = 28 yr<br>a: Same facility as Reference 65 |

*(Continued)*

**Table 1.** (*Continued*)

| Industry | N[a] | BeS [*n* (%)][b] | CBD [*n* (%)][c,d] | Comments |
|---|---|---|---|---|
| | | CP: 2 (2.7) | | b: Subjects with UP BeS included 1 with abnormal BAL BeLPT only, identified during previous bronchoscopy<br>d: Clinical evaluation for CBD offered to 5: 2 with confirmed abnormal BeLPTs (1 accepted – no CBD; 1 declined), 1 with single abnormal BeLPT (declined); 2 with symptoms but no abnormal BeLPTs (1 with CBD diagnosed; 1 – no CBD) |
| Nuclear weapons facility (36) | 2,221 | CP: 19 (0.9) | 2 (0.09) | Med data collected 1998–2002; Be operations 1953–1989; clean-up began 1990, decontamination and decommissioning began 1995; mean tenure = 13 yr<br>a: Participants were decontamination and decommissioning workers (about half hired pre- and half hired post-shutdown); same facility as References 29, 31, 45, and 107<br>d: 42% of subjects with BeS (8/19) evaluated with bronchoscopy |
| Copper-beryllium alloy finishing (37) | 153 | CP: 10 (6.5) | 6 (3.9) | Med data collected 2000; facility opened early 1950s; mean tenure = 16 yr<br>a: Same facility as Reference 49<br>b: Subjects with BeS included 1 with CBD diagnosed just before survey, 1 diagnosed shortly after survey; 9 with likely false abnormal BeLPTs were excluded; survey BeS including latter = 11.2% (17/152)<br>c: Subjects with CBD included 2 with disease diagnosed pre- and post-survey (*see* above)<br>d: 95% of subjects with BeS (18/19) evaluated with bronchoscopy |
| Copper-beryllium alloy service and distribution (38) | 88 | CP: 1 (1.1) | 1 (1.1) | Med data collected 2000–2001; facilities opened 1963, 1968, and 1972; mean tenure = 8 yr<br>a: Included workers from 3 service and distribution centers<br>d: 100% of subjects with BeS evaluated with bronchoscopy |
| Beryllium metal, alloy, and oxide production (55) | 264 | CP: 26 (9.8) | 6 (2.3) | Med data collected 1999; facility opened 1953; this report limited to those hired after 1993–1994 survey (33); mean tenure = 2 yr<br>a: Same facility as References 33 and 50<br>b: Subjects with BeS included 3 who were CP in 1997 (process-specific survey)<br>d: 77% of subjects with BeS (22/26) evaluated with bronchoscopy |
| Cross-sectional studies of current and former workers | | | | |
| Beryllia ceramics (39) | 505 | UP: 9 (1.8) | 9 (1.8) | Med data collected 1989–1992; facility manufactured ceramics 1958–1975, metalized ceramics (manufactured elsewhere) to time of study |
| | | CP: 8 (1.6) | | a: Included current and former workers<br>d: 100% of BeS (8/8) evaluated with bronchoscopy; study also included 10 with abnormal radiographs, 1 of whom had CBD diagnosed |
| Nuclear weapons facilities (40) | 3,842 | CP: 54 (1.4) | 5 (0.1) | Med data collected 1999–2002; Be used at Hanford 1954–1989, at Oak Ridge 1946–1960s, Savannah River Site |

(*Continued*)

**Table 1.** (*Continued*)

| Industry | N[a] | BeS [*n* (%)][b] | CBD [*n* (%)][c,d] | Comments |
|---|---|---|---|---|
| | | | | opened 1949; mean onsite tenure = 12 yr, 16 yr, and 12 yr, respectively<br>a: Construction trades workers; included current and former workers from 3 sites<br>c: CBD included: 2 with abnormal BAL BeLPT, and lymphocytosis; 1 with abnormal BALLPT and skin granulomas; 1 with normal BAL BeLPT, pathologic abnormalities (biopsy) and abnormal lung function; and 1 with information not presented<br>d: Number of subjects with BeS evaluated with bronchoscopy not reported, but authors stated 15% of those evaluated had CBD |
| Beryllium extraction, metal, and oxide production (41) | 577 | CP: 84 (14.6) | 44 (7.6) | Med data collected 1996–2001; facility opened 1957; mean tenure = 9 yr<br>a: Former workers only, employed between 1957 and 1978<br>c: Subjects with CBD included 12 with "probable" CBD (no granulomas but abnormal BALLPT and/or upper lobe fibrosis); 9 with disease diagnosed before study<br>d: 51% of subjects with BeS and/or abnormal radiographs (56/110) evaluated with bronchoscopy; information on evaluation for 9 with disease diagnosed presurvey not presented |
| Nuclear weapons facility (42) | 1,768 | CP: 23 (1.3) | N/A | Med data collected 2001–2005 (est); nuclear weapons test site operated 1951–1992<br>a: Former workers only, employed between 1951 and 1992<br>b: Only tested those with "high probability" of beryllium exposure<br>c: Authors reported that BeS referred for further evaluation but results not available |
| Nuclear weapons facility (57) | 1,875 | CP: 59 (3.1) | 5 (0.3) | Med data collected 1999–2005; research and development lab; mean tenure (n = 50) = 18 yr; mean hire-to-evaluation (n = 50) = 32 yr<br>a: Included current and former workers<br>c: CBD included 4 with granulomas, 1 with lymphocytosis, abnormal BAL BeLPT, and HCRT suggestive of sarcoidosis<br>d: 85% of subjects with BeS (50/59) clinically evaluated; 80% of latter (40/50) evaluated with bronchoscopy; 90% without bronchoscopy (9/10) no evidence of ILD on HRCT |
| Conventional munitions workers (43) | 570 | CP: 8 (1.5) | 0 (0.0) | Med data collected 2001–2008 (est); conventional munitions manufacture, testing and disassembly since 1941; nuclear weapons assembly onsite 1949–1975<br>a: Included current and former workers, employed in conventional munitions production through 2002; same facility as Reference 58; nuclear weapons workers excluded; mean tenure: BeS = 4 yr, non-BeS = 9 yr |

(*Continued*)

**Table 1.** (*Continued*)

| Industry | N[a] | BeS [*n (%)*][b] | CBD [*n (%)*][c,d] | Comments |
|---|---|---|---|---|
| | | | | b: BeS confirmed by second abnormal or borderline BeLPT<br>d: 75% of subjects with BeS (6/8) clinically evaluated, all without bronchoscopy |
| Nuclear weapons workers (58) | 1,004 | CP: 23 (2.3) | N/A | Med data collected 2001–2008 (est); conventional munitions manufacture, testing, and disassembly since 1941; nuclear weapons assembly onsite 1949–1975<br>a: Included current and former workers, employed in/exposed to nuclear weapons work; same facility as Reference 43; mean tenure = 11 yr<br>b: BeS confirmed by second abnormal or borderline BeLPT<br>c: Authors reported that subjects with BeS referred for further evaluation but results not available |
| Longitudinal studies with no baseline testing | | | | |
| Nuclear weapons facility (107) | 4,397 | CP: 107 (2.4) | 29 (0.7) | Med data collected 1991–1995; Be operations 1953–1989; tenure not reported<br>a: Study included initial testing plus follow-up 1 or 3 yr later for those with previous normal or UP BeLPT (n = 518); included both current and former workers; same facility as References 29, 31, 36, and 45<br>c: CBD included 12 with "probable" CBD (7 no granulomas, 5 no biopsy during bronchoscopy); CBD excluding latter = 0.4% (17/4,397)<br>d: Number of subjects with BeS evaluated with bronchoscopy not reported |
| Nuclear weapons facility (45) | 5,173 | CP: 235 (4.5) | 81 (1.6) | Med data collected 1991–1997; Be operations 1953–1989; tenure in 5-yr intervals (<5 to 40+ yr)<br>a: Study involved initial testing plus follow-up offered 3 yr later for those with previous normal or UP BeLPT (n = 2,891); included both current and former workers; same facility as References 29, 31, 36, and 107; data include results from Reference 107<br>c: CBD may have included some with "probable" CBD (unclear)<br>d: Number of subjects with BeS evaluated with bronchoscopy not reported |
| Precision machining of beryllium metal (46) | 235 | CP: 22 (9.4) | 13 (5.5) | Initial med data collected 1995–1997, follow-up 1997–1999; facility opened in 1969; tenure < 1–12 yr (initial survey)<br>a: Included current and daily contract workers; study involved initial testing plus up to 2 rounds of biennial follow-up<br>d: 86% of subjects with BeS (19/22) were clinically evaluated |
| Beryllia ceramics (47) | 136 | CP: 22 (16.2) | 15 (11.0) | Med data collected 1992–2003; facility opened 1981; tenure to diagnosis date, last BeLPT or termination date; mean tenure: CBD = 11 yr, BeS = 11 yr, non-BeS = 13 yr<br>a: Same facility as References 32, 34, and 48; 11-yr longitudinal follow-up of current and former workers from cohort |

(*Continued*)

**Table 1.** (*Continued*)

| Industry | N[a] | BeS [*n (%)*][b] | CBD [*n (%)*][c,d] | Comments |
|---|---|---|---|---|
| | | | | in Reference 32; data include results from References 32 and 34<br>b: BeS period prevalence adjusted for interval censoring was 20%<br>c: CBD period prevalence adjusted for interval censoring was 16%<br>d: Number of subjects with BeS evaluated with bronchoscopy not reported |
| Mining/extraction (65) | 120 | CP: 6 (5.0) | 2 (1.7) | Med data collected 1996–1997, 2001, and 2009; facility opened 1969; some previously worked at facility in Reference 33<br>a: Same facility as Reference 35; 3 current worker survey results combined: 1996-all workers eligible, 2001-hired after 1996 or declined in 1996 eligible, 2009-all workers eligible; 47 workers tested twice<br>b: Cumulative rate of BeS = 6.3%; BeS: 1996 = 3; 2001 = 2; 2009 = 1<br>d: *See* Reference 35 for clinical evaluations offered to 1996 participants; second person with CBD had BeS in 2001 and CBD in 2009; not reported if other 2 subjects with BeS from 2001 and 2009 evaluated with bronchoscopy |
| Longitudinal studies with baseline testing | | | | |
| Beryllia ceramics (48) | 97 | CP: 1 (1.0) | N/A | Med data collected 2000–2004; facility opened 1981, this group hired 2000–2004; mean tenure = 1 yr<br>a: Same facility as References 32, 34, and 47; all hired after start of comprehensive preventive program; BeLPT at hire and intervals thereafter (3, 6, 12, 24, 48 mo); at least one interval BeLPT needed for study<br>b: 4 abnormal at hire (1: CP at hire, UP at 3 mo, normal at 6 mo; 2: UP at hire, CP at 3 mo; 3: UP at hire, CP at 6 mo; 4: UP at hire, normal to 48 mo); for prevalence, to simulate cross-sectional survey used only final interval results; if all CP post-hire included, rate of BeS = 3.1% (3/97); BeS incidence = 0.7/1,000 person-mo (no at-hire abnormals), 2.7/1,000 person-mo (with at-hire abnormals)<br>c: Deidentified dataset used; information on possible CBD cases not provided |
| Copper-beryllium alloy finishing (49) | 82 | CP: 2 (2.4) | N/A | Med data collected 2000–2007; facility opened early 1950s, this group hired 2000–2006; mean tenure = 2 yr<br>a: Same facility as Reference 37; all hired after start of comprehensive preventive program; BeLPT at hire and intervals thereafter (3, 6, 12, 24, 48 mo); at least one interval BeLPT needed for study<br>b: 1 abnormal at hire (UP at hire, normal at 3 mo); for prevalence, to simulate cross-sectional survey used only final interval results; if all CP post-hire included, rate of BeS = 3.7% (3/82); BeS incidence = 1.9/1,000 person-mo<br>c: Deidentified dataset used; information on possible CBD cases not provided |

(*Continued*)

**Table 1.** (*Continued*)

| Industry | N[a] | BeS [*n (%)*][b] | CBD [*n (%)*][c,d] | Comments |
|---|---|---|---|---|
| Beryllium metal, alloy, and oxide production (50) | 290 | CP: 6 (2.1) | N/A | Med data collected 2000–2007; facility opened 1953; this group hired 2000–2006; median tenure = 2 yr<br>a: Same facility as References 33 and 55; all hired after start of comprehensive preventive program; BeLPT at hire and intervals thereafter (3, 6, 12, 24, 48 mo); at least one interval BeLPT needed for study<br>b: 2 abnormal at hire (CP at hire, normal at 6, 12 mo; UP at hire, CP at 24 mo); for prevalence, to simulate cross-sectional survey used only final interval results; if all CP post-hire included, rate of BeS = 3.8% (11/290); BeS incidence = 1.7/1,000 person-mo (no at-hire abnormals), 2.1/1,000 person-mo (with at-hire abnormals)<br>c: Deidentified dataset used; information on possible CBD cases not provided |

*Definition of abbreviations*: BAL = bronchoalveolar lavage; BALLPT = bronchoalveolar lavage lymphocyte proliferation test; Be = beryllium; BeLPT = beryllium lymphocyte proliferation test; BeS = beryllium sensitization; CBD = chronic beryllium disease; CP = confirmed positive (two or more abnormal BeLPTs); HCRT = high-resolution computed tomographic chest scan; ILD = interstitial lung disease; N/A = not applicable; UP = unconfirmed positive (single abnormal BeLPT).
Adapted by permission from Reference 51.
a. Number who participated, including BeLPT. *See* Comments for notes about study population.
b. BeS = beryllium sensitization; includes those also diagnosed with CBD. UP includes CPs when both UP and CP were reported. *See* Comments for additional notes about BeS.
c. *See* Comments for studies where diagnosis was not based on granulomas or other pathologic abnormalities consistent with CBD in biopsy samples, or where CBD was otherwise diagnosed (e.g., subsequent to radiographic abnormalities or symptoms, or abnormal BAL BeLPT).
d. *See* Comments for percentage of BeS who were clinically evaluated for CBD using bronchoscopy and transbronchial biopsy subsequent to BeS; alternatives noted.

In addition, this program recommended annual testing for workers exposed or with potential exposure to beryllium. In 2009, the American Council of Governmental Industrial Hygienists adopted a threshold limit value to prevent BeS of 0.05 $\mu g/m^3$ inhalable beryllium averaged over an 8-hour period (27).

The BeLPT has become the primary screening tool in the workplace for BeS and CBD (28–30). Cross-sectional studies of workers in various U.S. industries have found that the prevalence of BeS ranged from 0.9 to 14.6%, and the prevalence of CBD ranged from 0.0 to 7.8% (29, 31–43, 55, 57, 58) (Table 1). Longitudinal studies of defined cohorts showed that 1.0 to 16.2% of exposed workers developed BeS over time, and 0.0 to 11.0% developed CBD (44–47, 52, 53, 65). Longitudinal studies of workers hired after a comprehensive preventive program showed lower levels of BeS (48–50). Some studies suggested that the risk of progression from BeS to CBD may be highest in the early years and decline over time (54), although BeS and CBD can occur years after first exposure.

Table 3 lists specific jobs or work processes associated with BeS and CBD. 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 (51).

In a study of exposure–response relationships in a manufacturing plant, a job-exposure matrix was derived from a substantial set of personal exposure estimates and extensive historical exposure data. The matrix was then combined with

**Table 2.** Checklist of Document Development Methods

| | Yes | No |
|---|---|---|
| Panel assembly | | |
| Included experts from relevant clinical and nonclinical disciplines | X | |
| Included individual who represents patients and society at large | | X |
| Included methodologist with appropriate expertise | | X |
| Literature review | | |
| Performed in collaboration with a librarian | | X |
| Searched multiple electronic databases | | X |
| Reviewed reference lists of retrieved articles | X | |
| Evidence synthesis | | |
| Applied prespecified inclusion and exclusion criteria | | X |
| Evaluated included studies for sources of bias | X | |
| Explicitly summarized benefits and harms | | N/A |
| Used PRISMA to report systematic review | | N/A |
| Used GRADE to describe quality of evidence | | N/A |
| Generation of recommendations | | |
| Used GRADE to rate the strength of recommendations | | N/A |

*Definition of abbreviations*: GRADE = Grading of Recommendations Assessment, Development and Evaluation; N/A = not applicable; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table 3.** Process-related Risk of Beryllium Sensitization and Chronic Beryllium Disease by Type of Industry[a]

| Industry (Reference) | Job or Process | BeS (%) | CBD (%) |
|---|---|---|---|
| Nuclear weapons facility (31)* | Machinists | 4.7 | N/A |
| | Metallurgical operator | 4.6 | |
| Beryllia ceramics (39) | Dry pressing | 15.8 | 15.8 |
| | Process development/engineering | 13.6 | 13.6 |
| | Ventilation maintenance | 11.1 | 11.1 |
| Beryllia ceramics (32)[†] | Lapping[‡] | 20.0 | N/A |
| | Machining | 14.3 | |
| Beryllium metal, alloy and oxide production (33)[§] | Ceramics production | 11.6 | 9.0 |
| | Beryllium metal pebble plant[‖] | 13.4 | 5.2 |
| | Analytic laboratory[¶] | 20.0 | 4.0** |
| Beryllia ceramics (34)[†,††] | Lapping | 21.1 | N/A |
| | Machining | 17.5 | |
| | Forming | 15.6 | |
| | Firing | 14.9 | |
| Nuclear weapons facility (45)* | Beryllium machinists | 11.9 | 8.5 |
| | Health physics | 11.9 | 4.8 |
| | Construction trade | 10.0 | 2.6 |
| Copper-beryllium alloy finishing (37) | Point and chamfer[‡‡] | 21.4 | 21.4 |
| | Wire pickling and annealing | 12.5 | 10.3 |
| | Wire drawing | 13.6 | 9.5 |
| Beryllium metal, alloy, and oxide production (55)[§,§§] | Be metal pebbles plant/Be oxide | 26.9 | 5.0** |
| | Alloy melting and casting | 14.8 | 5.2 |
| | Maintenance | 18.0 | 2.4** |

*Definition of abbreviations*: Be = beryllium; BeS = beryllium sensitization; CBD = chronic beryllium disease; N/A = not applicable.
Results presented are significant at the $P < 0.10$ or lower level. Adapted by permission from Reference 51.
*Same facility (31, 45).
†Same facility (32, 34).
‡Lapping is a machining operation, in which two surfaces are rubbed together with a liquid containing an abrasive grit.
§Same facility (33, 55).
‖All ceramics workers removed from this analysis.
¶All ceramics and pebble plant workers removed from this analysis.
**Results not significant.
††Results are for longer-term workers (employed ⩾6 yr; first surveyed in 1992 but none BeS at that time).
‡‡Chamfer (here) is the process of putting a beveled edge on a rod.
§§Results are for shorter-term workers (employed ⩽6 yr).

work histories to create individual estimates of average, cumulative, and highest-job-worked exposure for both total mass concentration and smaller particles more likely to be deposited in the alveolar region of the lung (i.e., respirable and submicron mass concentrations) (55). Both the total and respirable beryllium mass concentration estimates were associated with BeS (average and highest-job-worked exposure) and CBD (cumulative exposure). However, exposure-response relationships have been inconsistent across studies. No association was found in some studies, whereas the association did not reach statistical significance in other studies (i.e., the effect would have been clinically important if real, but the confidence intervals were wide due to relatively few events and included no effect) (33, 34, 56). This suggests that individual susceptibility factors also play a role. Multiple workplace studies identified some workers with BeS or CBD who had apparent minimal or bystander exposure (32–34, 40, 45, 46, 57, 58), and one report described cases of CBD diagnosed among non–occupationally-exposed individuals living near a beryllium production facility (59), providing evidence that low-level exposures may lead to CBD (60). What is clear from the existing evidence is that a permissible exposure limit of 2 $\mu g/m^3$ does not prevent BeS and CBD (25, 33, 34, 46, 51, 55, 56).

Because a clear relationship between airborne beryllium level and risk of BeS and CBD has not been established, other routes (e.g., dermal) and/or factors may be important in determining sensitization to beryllium (51, 54, 61–72). As an example, solubility and size of the beryllium particles likely affect risk of BeS and CBD (62, 63, 65–68, 73). Exposure to poorly soluble materials such as beryllium oxide or oxide-coated metal appears to be associated with risk of CBD (37, 47, 66–68); beryllium in these forms persists in the body for years (69–72). Very small (i.e., ⩽2.5 μm) particles penetrate to the deep lung and are associated with increased risk of CBD (55, 73).

## Genetic Susceptibility

Genetic susceptibility contributes to the development of BeS and progression of BeS to CBD (74). CBD is characterized by an accumulation of beryllium-specific $CD4^+$ T cells in the lung (28, 75–78). These T cells recognize beryllium in a major histocompatibility complex class II (MHC II)-restricted manner (76), and multiple studies have confirmed that a polymorphism of the HLA-DP $\beta_1$-chain gene is strongly associated with susceptibility to beryllium-induced disease (79–87). *HLA-DPB1* alleles coding for a glutamic acid residue at position 69 of the β-chain ($Glu^{69}$) are associated with increased risk of both BeS and CBD, with odds ratios greater than 10 (74, 79, 87). But all Glu69 alleles do not confer equal risk, as those with greater negative surface charge (i.e., greater binding affinity) are related to increased risk of CBD (80). Because approximately 25% of patients with CBD do not carry the HLA-DP $Glu^{69}$ gene variant, other genetic factors may be important in BeS, progression to CBD, and disease severity (81, 83, 84, 88).

One study reported that both the presence of the HLA-DPβ $Glu^{69}$ gene variant and higher-level exposure to beryllium were associated with increased risk of CBD and BeS, with the combination associated with a multiplicative increase in risk (89). In another cohort of beryllium-exposed workers, both genetic factors and higher exposure contributed to risk of CBD, but only the former appeared to be associated with BeS (90).

## Immunopathogenesis

$CD4^+$ T cells play a critical role in the immunopathogenesis of CBD (75–78, 91–94). Activation of beryllium-specific $CD4^+$ T cells requires engagement of a surface T-cell receptor with an MHC II molecule on the surface of antigen-presenting cells in the presence of beryllium (78) (Figure 1). BAL $CD4^+$ T cells from patients with CBD are composed of oligoclonal expansions specific for beryllium and compartmentalized to lung (78, 91). Beryllium-responsive $CD4^+$ T cells secrete Th1-type cytokines, such as IL-2, IFN-γ, and tumor necrosis factor-α (TNF-α) (78, 95). The release of IFN-γ and TNF-α is believed to promote the accumulation, activation, and aggregation of macrophages, resulting in the development of granulomatous inflammation. Experimental studies have demonstrated that HLA molecules can present beryllium to beryllium-specific $CD4^+$ T cells (4, 88, 93, 97).

## Pathology

As in sarcoidosis, the characteristic pathologic lesion in CBD is the noncaseating granuloma (97–100), consisting of an aggregate of epithelioid histiocytes (transformed macrophages) with a collar of lymphocytes (predominantly $CD4^+$ T cells) and scattered plasma cells. Multinucleated giant cells, formed by fusion of epithelioid histiocytes, are usually present. The morphology of the granuloma may vary from a loosely formed collection of a few epithelioid histiocytes with scattered lymphocytes to a well-formed one. Fibrosis may develop, and foreign-body granulomas are sometimes seen. The distribution of the granulomas within the lung follows the pattern of sarcoidosis: in the subpleural area, around bronchovascular bundles, and within interlobular septae.

An interstitial mononuclear cell infiltrate may be found in CBD that is composed of lymphocytes and variable numbers of plasma cells. The extent of this infiltrate may correlate with lymphocytosis in the BAL. Detection of beryllium in tissue samples was at one time part of the diagnostic algorithm for CBD, but this is no longer necessary. Nonetheless, beryllium-containing particles can be demonstrated within CBD granulomas (101–103).

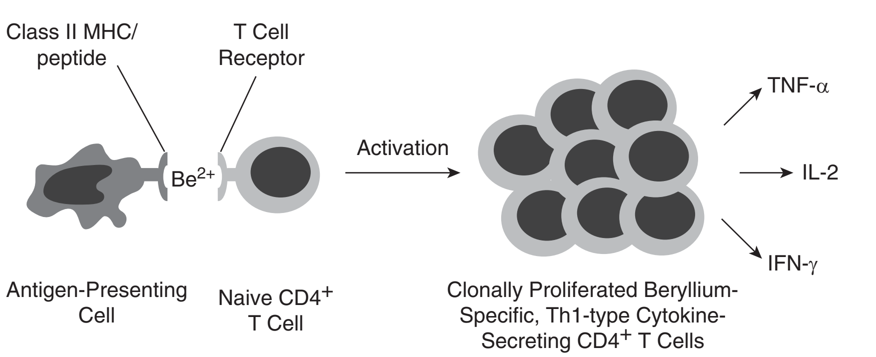


**Figure 1.** Immune response to beryllium. After the inhalation of beryllium-containing particulates, antigen-presenting cells expressing the major histocompatibility complex (MHC) molecule, HLA-DP, with a glutamic acid at amino acid position 69 of the β-chain present beryllium to $CD4^+$ T cells. This results in T-cell activation, proliferation, and Th1-type cytokine production (e.g., IFN-γ, IL-2, and tumor necrosis factor [TNF]-α). IFN-γ and TNF-α promote macrophage accumulation, activation, and aggregation, which lead to the development of granulomatous inflammation and eventually lung fibrosis.

## Diagnostic Criteria

### BeLPT

Because BeS is the result of a beryllium-specific cell-mediated immune response, the blood BeLPT is the primary diagnostic tool (28–30, 104, 105). The BeLPT can be used in medical surveillance to detect workers with CBD who have no clinical manifestations (29, 51, 52, 106, 107).

The BeLPT is typically performed in an experienced laboratory. A limited number of laboratories perform the test in the United States, Canada, and Europe. Mononuclear cells are isolated from heparinized peripheral venous blood or BAL fluid and placed in culture in the presence and absence of beryllium sulfate, across a three-log range of salt concentrations. Cell proliferation is measured by the incorporation of tritiated thymidine into dividing cells at two different time points, after Day 4 or 5 and Day 6 or 7 in culture. Positive control samples are incubated with nonspecific mitogens, such as phytohemagglutinin A or concanavalin A, or antigens, such as tetanus toxoid or *Candida albicans*. Results are expressed as a stimulation index, the ratio of the counts per minute of radioactivity in cells stimulated with beryllium salts divided by the counts per minute for unstimulated cells (108).

Tests are considered "uninterpretable" if they are unable to be identified as abnormal or normal due to high unstimulated control cell counts, lack of a response to positive controls, or high variability within beryllium-exposed wells. Because the BeLPT is a bioassay with considerable inherent and interlaboratory variability, the test is usually repeated to confirm the initial result (107, 109). In an effort to decrease test variability, the DOE published a consensus standard on BeLPT assay materials and procedures in 2001 (110).

A BeLPT is considered "abnormal" if two or more of the six stimulation indices exceed the normal range. A test is considered "borderline" and retesting performed if only one of the six stimulation indices exceeds the normal range. This is based on the results of several studies that have highlighted the variability of the BeLPT and shown increased specificity with the use of these criteria (107, 109, 111, 112).

There is no gold standard for BeS. Therefore, receiver operator characteristics for the BeLPT can only be estimated. CBD based on histology or two abnormal BeLPTs has been used as the standard from which to estimate receiver operator characteristics. Estimates of the test's sensitivity for BeS and CBD range widely (30, 31, 34, 39, 44, 107, 113–115). In an analysis of DOE surveillance data (97), the "sensitivity" of a single BeLPT for BeS (defined as two abnormal BeLPTs) was 68.3%, and the "specificity" was 96.9%. Reanalysis of the DOE data found both high specificity and sensitivity when a modified approach was used to interpret the BeLPT results (i.e., an initial abnormal test was confirmed with either an abnormal or borderline result from a repeat blood sample that was split between two laboratories) (111, 112). An enhanced algorithm (i.e., both the initial and repeat blood samples were split, and the criterion for BeS was at least one abnormal test and one borderline test) improved the sensitivity of the BeLPT to 88% without sacrificing specificity (111).

Another test for the presence of a beryllium-specific immune response is the beryllium patch test. Use of the patch test is primarily historic, because it can lead to sensitization in beryllium-naive individuals (116).

### Diagnostic Criteria for BeS

Individuals who have evidence of a beryllium-specific immune response, but who have no evidence of beryllium-related lung disease, are considered to have BeS without CBD (106, 108, 117). A diagnosis of BeS is supported by two abnormal blood BeLPTs, one abnormal BAL BeLPT, or a positive skin patch test to beryllium (although the last presents the risk of inducing sensitization).

A borderline BeLPT result is generally repeated, with split samples being sent to two different laboratories. Based on the data cited above (111), a National Academies of Science committee recommended that a borderline BeLPT result combined with an abnormal result also be considered indicative of BeS (118). We agree that a diagnosis of BeS may be based on either two abnormal BeLPTs or one abnormal BeLPT plus one borderline BeLPT. This is based on analysis of the DOE medical surveillance program data (111, 112). Three borderline BeLPTs may also indicate sensitization (119).

### Diagnostic Criteria for CBD

A diagnosis of CBD is based on confirmation of an immune response to beryllium (described above) and granulomatous lung inflammation on lung biopsy (120). Depending on the clinical setting, feasibility of certain diagnostic tests, and degree of diagnostic certainty needed, probable CBD can be diagnosed based on differing combinations of diagnostic criteria, including a clinical presentation consistent with CBD, a history of beryllium exposure, evidence of BeS (e.g., abnormal BeLPT), radiographic findings, lung histology, BAL findings, and PFT abnormalities. For example, when BeS is confirmed but a lung biopsy is not done or is not possible, a probable diagnosis of CBD can be based on imaging consistent with sarcoidosis or a BAL lymphocytosis. This classification is based on the long-established use of these criteria in the beryllium disease literature (118, 120). It should be recognized that certain diagnostic findings (e.g., an abnormal BeLPT, lung granulomas) lead to greater diagnostic certainty than others (e.g., nonspecific interstitial changes on chest radiographs or pulmonary function deficits).

The U.S. Department of Labor (DOL) has specific diagnostic criteria for current or former workers at DOE facilities applying for compensation due to a diagnosis of CBD (121).

## Evaluation

### Clinical Manifestations of BeS and CBD

BeS and CBD cases are increasingly being identified when the individual is still relatively asymptomatic, with normal lung function and chest imaging, due to workplace surveillance programs using the blood BeLPT (36, 106, 108, 122). However, progression to severe illness still occurs (123, 124). Symptom onset is insidious in CBD and may include exertional dyspnea, fatigue, cough, and chest discomfort (123, 125–127). Patients with early disease typically have a normal physical examination, with inspiratory crackles developing if the disease progresses (39, 120). Symptoms and signs may emerge many years after cessation of exposure to beryllium.

PFT can show obstruction, restriction, a mixed process, and/or an isolated reduced diffusing capacity for carbon monoxide, with obstruction being the most common (128–130). Normal PFT is also common, especially in cases of subclinical disease initially identified by BeLPT (130). Cardiopulmonary exercise testing may detect both ventilatory and gas exchange abnormalities (130).

The appearance of CBD on chest radiographs is similar to that of sarcoidosis, although mediastinal or hilar lymphadenopathy is less common and is usually seen in the presence of parenchymal opacities (131). On chest CT scan, nodules are the most common finding, often clustered around the bronchi, within interlobular septa, or in the subpleural region. Ground-glass opacities, bronchial wall thickening, and thickening of interlobular septa are also seen (131–135). In advanced disease, honeycombing, subpleural cysts, calcification, and conglomerate masses may be found.

The lung is the primary organ affected by CBD. Extrathoracic organ involvement occurs (123, 125–127), but it is rarely clinically important (Table 4). In fact, most extrathoracic manifestations of CBD were reported before the BeLPT came into use and are not seen in the modern era.

### Diagnostic Evaluation for BeS and CBD

A diagnostic evaluation for BeS and CBD is generally prompted by a history of exposure to beryllium (although known exposure is not necessary for the diagnosis of BeS or CBD), suspicion of sarcoidosis (because up to 6% of all patients diagnosed with sarcoidosis actually have CBD) (6, 136, 137), or the identification of interstitial lung disease. A thorough occupational history is obtained from all patients being evaluated for BeS and CBD. The history includes questions regarding beryllium or metal exposure and work in industries with known beryllium use (Table 5). The latency between exposure and disease can be long (34, 44, 46, 52), and BeS and CBD have

**Table 4.** Clinical Differences between Sarcoidosis and Chronic Beryllium Disease

| Clinical Finding | CBD | Sarcoidosis |
|---|---|---|
| Beryllium lymphocyte proliferation test | Abnormal | Normal |
| Ophthalmologic | Conjunctivitis only | Conjunctivitis, uveitis, retinal involvement |
| Erythema nodosum | No | Yes |
| Lupus pernio | No | Yes |
| Onset | Insidious | Acute or insidious |
| Neurologic involvement | None | Can involve the central or peripheral nervous system |
| Cardiac involvement | Rare | Occasional |
| Hepatic involvement | Occasional | Common |
| Isolated hilar adenopathy | Very rare | Common |
| Extrapulmonary manifestations without pulmonary involvement | No | Yes |

*Definition of abbreviation*: CBD = chronic beryllium disease.

been reported in individuals with seemingly minimal exposures (31, 33, 39, 44, 52, 59); thus, BeS and CBD are considered in any individual with a history of beryllium or metal exposure or work in a beryllium-using industry, even if long ago.

Evaluation for BeS and CBD begins with a BeLPT. Individuals with BeS are further evaluated with PFT and chest imaging (either a chest radiograph or chest CT scan). The decision of whether or not to also perform bronchoscopy in patients with BeS is made on a case-by-case basis. Criteria favoring bronchoscopy include: absence of contraindications, evidence of pulmonary function abnormalities, evidence of abnormalities on chest imaging, and personal preference of the patient. This approach has been used for sarcoidosis for many years (138).

Patients with a negative bronchoscopy remain at risk for the subsequent development of disease and require ongoing follow-up (52).

Tissue sampling is controversial in patients with BeS who have no pulmonary function or radiographic abnormalities. Arguing for tissue sampling is that the sensitivity and specificity of PFT and chest imaging for the confirmation of CBD are less than that of bronchoscopy with transbronchial biopsy (14–100% of patients with BeS have CBD on histologic examination of lung tissue at the time of their initial evaluation [52, 108, 109]). Confirmation of CBD determines disease status and guides subsequent management. Arguing against tissue sampling is that treatment will not be initiated until the patient develops lung function abnormalities (57).

Bronchoscopy typically includes both BAL and transbronchial biopsies. BAL fluid is sent for the following: mycobacterial and fungal studies, differential cell count to detect lymphocytic alveolitis, and a BeLPT. A large-volume (240–480 ml) lavage is usually performed (e.g., four 30–60 ml aliquots in each of the two subsegments of the middle lobe or lingula) to obtain sufficient viable lymphocytes for the BeLPT (26, 28, 120). The BAL fluid must be rapidly processed so that cells can be shipped to the laboratory without delay.

Although the BAL BeLPT can be helpful in the diagnosis of CBD, especially when the blood BeLPT is normal, the test is not always abnormal in patients with CBD who have abnormal blood BeLPT results and granulomatous inflammation on lung biopsy. The BAL BeLPT can be normal in smokers with CBD (139) and those on immunosuppressive medications. BAL typically reveals a lymphocytosis in CBD, with values greater than 20% (106, 140). The percentage of BAL lymphocytes and BAL BeLPT results may have prognostic value (52, 141).

Transbronchial biopsies are performed to establish the presence of granulomas and/or mononuclear interstitial infiltrates consistent with CBD. The number of lung tissue pieces needed for a definitive evaluation for CBD has not been formally studied, but a similar approach to that used for sarcoidosis is reasonable (100). Histochemical studies for fungal and mycobacterial organisms should be performed to rule out infectious granulomatous disease.

In addition to sarcoidosis, the differential diagnosis also includes tuberculosis, atypical mycobacterial infections, hypersensitivity pneumonitis, granulomatous disease due to other metals like aluminum or titanium, and idiopathic pulmonary fibrosis. CBD is differentiated from these diseases by the demonstration of a beryllium-specific immune response.

## Natural History and Management

### Natural History and Management of BeS

Two overlapping case series reported that the rate of progression from BeS to CBD is as high as 8.8% over a period of up to 20 years (52, 143). However, other studies have found little or no evidence of progression from BeS to CBD (83, 144).

Periodic medical evaluation is performed on individuals with BeS every 2 to 3 years and potentially yearly if there is concern regarding disease progression (142), to determine whether or not there has been progression from BeS to CBD. The evaluation includes a review of symptoms, physical examination, and PFT (117, 118). These are followed by a chest CT scan if pulmonary function has deteriorated. Bronchoscopy is performed on a case-by-case basis, as described above. This approach is based on the committee's collective experience in monitoring patients with BeS in occupational health surveillance programs (52, 143, 144).

Whether or not continued exposure increases the risk of progression from BeS to disease is not known. However, the possibility that continued exposure is a contributing factor (53) is supported by the observations that machinists may have a higher risk of progression (52), individuals with an abnormal blood BeLPT are less likely to have CBD at the time of their initial evaluation if they work in low-exposure settings (34, 40), and two studies of nuclear weapons workers have demonstrated increased risk of CBD with higher cumulative exposures (89, 90). Based on the limited evidence about determinants of progression, it seems prudent for workers with BeS to avoid all future occupational exposures to beryllium, even

**Table 5.** Industries and Jobs with Potential Beryllium Exposure

| Industry Category | Industries by NAICS Codes with Potential Beryllium Exposure ⩾ 0.1 μg/m³* NAICS Industry Description | Examples of Jobs with Potential Beryllium Exposure within the Industry Category† | Related Products Possibly Containing Beryllium within the Industry Category (Partial Listing) |
|---|---|---|---|
| Aerospace | Fluid power valve & hose fitting manufacturing | Deburr worker | Aircraft & spacecraft spare parts |
| | Aircraft manufacturing | Grinder | Altimeters |
| | Other aircraft part & auxiliary equipment manufacturing | Holder | Braking systems |
| | Other guided missile & space vehicle parts & auxiliary equipment manufacturing | Janitor | Bushings & bearings for landing gear |
| | Air traffic control | Lapper | Bushings on aircraft |
| | Other airport operations | Machinist | Electrical insulators |
| | Other support activities for air transportation | Welder | Electronic & electrical connectors |
| | Research & development in the physical, engineering, & life sciences | | Engines |
| | Janitorial services | | Gyroscopes |
| | Reupholstery & furniture repair | | Landing gear |
| | | | Mirror support structures |
| | | | Mirrors (e.g. space telescopes) |
| | | | Missile guidance systems |
| | | | Precision tools |
| | | | Resistor cores |
| | | | Rockets |
| | | | Satellites |
| | | | Secondary support structures for satellites & space vehicles |
| | | | Structural components |
| Automotive | Industrial truck, tractor, trailer, & stacker machinery manufacturing | Abrasive blaster | Abrasive blasting media made from coal or copper slag |
| | | | Air-bag triggers |
| | Automobile manufacturing | Booth blaster | Anti-lock brake system terminals |
| | Light truck & utility vehicle manufacturing | Maintenance | Electrical insulators in ignition systems |
| | Heavy-duty truck manufacturing | MIG welder | Electronic & electrical connectors |
| | Motor vehicle body manufacturing | Painter | Formula-1 race car parts |
| | Truck trailer manufacturing | Prep shop | Steering wheel connecting springs |
| | Motor home manufacturing | Ring welder | Valve seats for drag racer engines |
| | Travel trailer & camper manufacturing | Spray painter | |
| | Gasoline engine & engine parts manufacturing | Welder | |
| | Other motor vehicle electrical & electronic equipment manufacturing | | |
| | Motor vehicle steering & suspension components (except spring) manufacturing | | |
| | Motor vehicle brake system manufacturing | | |
| | Motor vehicle transmission & power train parts manufacturing | | |
| | Motor vehicle metal stamping | | |
| | All other motor vehicle parts manufacturing | | |

*(Continued)*

**Table 5.** (*Continued*)

| Industry Category | Industries by NAICS Codes with Potential Beryllium Exposure $\geqslant 0.1\ \mu g/m^3$* NAICS Industry Description | Examples of Jobs with Potential Beryllium Exposure within the Industry Category† | Related Products Possibly Containing Beryllium within the Industry Category (Partial Listing) |
|---|---|---|---|
| | All other transportation equipment manufacturing | | |
| | General automotive repair | | |
| | Automotive body, paint, & interior repair & maintenance | | |
| Biomedical | Dental laboratories | Caster | Dental bridges |
| | Dental equipment & supplies manufacturing | Cutter/grinder | Foil masks in X-ray lithography |
| | Other medical imaging equipment manufacture | Dental technician | Medical laser & scanning electron microscope components |
| | | Induction melter | Medical lasers |
| | | Maintenance technician | Partials & other dental prostheses |
| | | | X-ray tube windows |
| | | | X-ray windows |
| | | | X-ray windows in radiation monitors |
| Mining | Support activities for metal mining | Driller | |
| | Site preparation contractors | Painter | |
| | Mining machinery & equipment manufacturing | | |
| | Geophysical surveying & mapping services | | |
| Primary metal manufacturing | | Abrasive cut-off saw operator | Beryllium oxide powder, beryllium oxide ceramics, beryllium metal, copper-beryllium alloys, aluminum-beryllium metal matrices, beryllium hydroxide, beryllium fluoride |
| | | Administrative worker | |
| | | Alloy arc furnace worker | |
| | | Belt sander | |
| | | Bench grinder | |
| | | Beryllium control lab technician | |
| | | Beryllium furnace operator | |
| | | Beryllium hydrolysis operator | |
| | | Beryllium instrument lab technician | |
| | | Chemical finisher | |
| | | Cutter | |
| | | Electrical discharge machinist | |
| | | Engineer | |
| | | Flow lines operator | |
| | | Furnace charge worker | |
| | | Furnace operator | |
| | | Furnace rebuild worker | |
| | | Gas bearings operator | |
| | | Grinder | |
| | | Inspector | |
| | | Lapper | |
| | | Lathe operator | |
| | | Leach operator | |
| | | Machinist | |
| | | Maintenance worker | |
| | | Mill and NC mill operator | |
| | | Optics worker | |
| | | Ore processor | |

(*Continued*)

**Table 5.** (*Continued*)

| Industry Category | Industries by NAICS Codes with Potential Beryllium Exposure ⩾ 0.1 μg/m³* NAICS Industry Description | Examples of Jobs with Potential Beryllium Exposure within the Industry Category† | Related Products Possibly Containing Beryllium within the Industry Category (Partial Listing) |
|---|---|---|---|
| | | Product controller & inventory controller | |
| | | Sulfate mill operator | |
| | | SX operator | |
| | | Thickener operator | |
| | | Wet grind operator | |
| Manufacturing/consumer products | Natural gas liquid extraction | Abrasive blaster | Abrasive blasting media made from coal or copper slag |
| | | | Bearings |
| | All other miscellaneous textile product mills | Artist | Bellows |
| | Wood preservation | Ash handler | Beryl & chrysoberyl gemstones (including aquamarine, emerald & alexandrite) |
| | Paper (except newsprint) mills | Assistant operator | Bicycle frames |
| | Newsprint mills | Auto line operator | Camera shutters |
| | Paperboard mills | Ball mill operator | Cellular telephone components |
| | Laminated aluminum foil manufacturing for flexible packaging uses | Bencher | Clock & watch gears & springs |
| | All other petroleum & coal products manufacturing | Billet handler | Commercial phonograph styluses |
| | Petrochemical manufacturing | Blaster | Commercial speaker domes |
| | Industrial gas manufacturing | Blender | Computer disk drives |
| | Inorganic dye & pigment manufacturing | Brazer | Diamond drill bit matrices |
| | All other basic inorganic chemical manufacturing | Caster | Disk drive arms |
| | Cyclic crude & intermediate manufacturing | Caster helper | Electrical insulators in base stations & cell phones |
| | Ethyl alcohol manufacturing | Ceramics grinder | Electromagnetic shields |
| | All other basic organic chemical manufacturing | Chemical operator | Electronic & electrical connectors |
| | Pharmaceutical preparation manufacturing | Conveyor | Fishing rods |
| | Paint & coating manufacturing | Conveyor operator | Golf clubs |
| | Surface active agent manufacturing | Crane operator | Injection molds for plastics |
| | Custom compounding of purchased resins | Cutter | Integrated circuit chip carriers in super computers |
| | All other miscellaneous chemical product & preparation manufacturing | Engine tester | Jewelry |
| | Unlaminated plastics profile shape manufacturing | Filter worker | Manmade emerald & gemstones with distinctive colors |
| | Plastics pipe & pipe fitting manufacturing | Finish grinder | Musical instrument valve springs |
| | All other plastics product manufacturing | Finisher | Nonsparking tools |
| | Vitreous china plumbing fixture & china & earthenware bathroom accessories manufacturing | Fitter | Pen clips |
| | Nonclay refractory manufacturing | Foreman | Personal computer components |
| | Other pressed & blown glass & glassware manufacturing | Foundry tender | Plastic molds |
| | Glass product manufacturing made of purchased glass | Foundry worker | Plunger tips for die-casting machines |
| | Concrete pipe manufacturing | Furnace attendant | Precision motion control for automation equipment |

(*Continued*)

**Table 5.** (*Continued*)

| Industry Category | Industries by NAICS Codes with Potential Beryllium Exposure ⩾ 0.1 μg/m$^3$* NAICS Industry Description | Examples of Jobs with Potential Beryllium Exposure within the Industry Category† | Related Products Possibly Containing Beryllium within the Industry Category (Partial Listing) |
|---|---|---|---|
| | Other concrete product manufacturing | Furnace helper | Radio & laser tubes |
| | All other miscellaneous nonmetallic mineral product manufacturing | Furnace operator | Repeater housings on transoceanic cables |
| | Iron & steel mills | General manager | Rotary telephone springs & connectors |
| | Iron & steel pipe & tube manufacturing from purchased steel | Grind operator | Sprinkler system springs |
| | Rolled steel shape manufacturing | Grinder | Sprinkler system washers |
| | Alumina refining | Ground coat sprayer | Switches & springs |
| | Secondary smelting & alloying of aluminum | Hot press operator | Transistor mountings (integrated circuit substrates) |
| | Aluminum sheet, plate, & foil manufacturing | Incinerator operator | Welding electrodes, including bertrandite gemstone electrodes |
| | Primary smelting & refining of nonferrous metal (except copper & aluminum) | Laborer | |
| | Copper rolling, drawing, & extruding | Lathe operator | |
| | Secondary smelting, refining, & alloying of copper | Lead man atomization | |
| | Nonferrous metal (except copper & aluminum) rolling, drawing, & extruding | Machine operator | |
| | Secondary smelting, refining, & alloying of nonferrous metal (except copper & aluminum) | Machinist | |
| | Steel foundries (except investment) | Maintenance | |
| | Aluminum die-casting foundries | Melter | |
| | Nonferrous (except aluminum) die-casting foundries | Metal conditioner | |
| | Aluminum foundries (except die-casting) | MIG/TIG welder | |
| | Copper foundries (except die-casting) | Miller | |
| | Other nonferrous foundries (except die-casting) | Modeling | |
| | Metal stamping | Mold assembler | |
| | Powder metallurgy part manufacturing | Mold maker | |
| | Hand & edge tool manufacturing | Operator | |
| | Kitchen utensil, pot, & pan manufacturing | Operator-alloy | |
| | Fabricated structural metal manufacturing | Painter | |
| | Plate work manufacturing | Panel welder | |
| | Metal window & door manufacturing | Pebbles operator | |
| | Sheet metal work manufacturing | Plasma arc | |
| | Ornamental & architectural metal work manufacturing | Plasma cutter | |
| | Power boiler & heat exchanger manufacturing | Plater | |

(*Continued*)

**Table 5.** (*Continued*)

| Industry Category | Industries by NAICS Codes with Potential Beryllium Exposure $\geq$ 0.1 $\mu g/m^3$* NAICS Industry Description | Examples of Jobs with Potential Beryllium Exposure within the Industry Category† | Related Products Possibly Containing Beryllium within the Industry Category (Partial Listing) |
|---|---|---|---|
| | Metal tank (heavy gauge) manufacturing | Plating | |
| | Metal can manufacturing | Polisher | |
| | Other metal container manufacturing | Pourer | |
| | Hardware manufacturing | Power coater | |
| | Machine shops | Production operator | |
| | Bolt, nut, screw, rivet, & washer manufacturing | Rotoblast worker | |
| | Metal coating, engraving (except jewelry & silverware), & allied services to manufacturers | Sandblaster | |
| | Electroplating, plating, polishing, anodizing, & coloring | Sandblaster primer | |
| | Other metal valve & pipe fitting manufacturing | Saw operator | |
| | Ammunition (except small arms) manufacturing | Shredder feeder helper | |
| | Fabricated pipe & pipe fitting manufacturing | Shredder operator | |
| | Enameled iron & metal sanitary ware manufacturing | Slotter operator | |
| | All other miscellaneous fabricated metal product manufacturing | Solder assembly work | |
| | Farm machinery & equipment manufacturing | Solderer | |
| | Lawn & garden tractor & home lawn & garden equipment manufacturing | Stick welder | |
| | Construction machinery manufacturing | Technician | |
| | Plastics & rubber industry machinery manufacturing | Tool & die maker | |
| | Semiconductor machinery manufacturing | Tube cutter | |
| | All other industrial machinery manufacturing | Turf cutter | |
| | Other commercial & service industry machinery manufacturing | Welder | |
| | Heating equipment (except warm air furnaces) manufacturing | | |
| | Air-conditioning & warm air heating equipment & commercial & industrial refrigeration equipment manufacturing | | |
| | Industrial mold manufacturing | | |
| | Machine tool (metal cutting types) manufacturing | | |
| | Special die & tool, die set, jig, & fixture manufacturing | | |
| | Cutting tool & machine tool accessory manufacturing | | |
| | Turbine & turbine generator set units manufacturing | | |
| | Other engine equipment manufacturing | | |

*(Continued)*

**Table 5.** (*Continued*)

| Industry Category | Industries by NAICS Codes with Potential Beryllium Exposure ⩾ 0.1 μg/m³* NAICS Industry Description | Examples of Jobs with Potential Beryllium Exposure within the Industry Category† | Related Products Possibly Containing Beryllium within the Industry Category (Partial Listing) |
|---|---|---|---|
| | Pump & pumping equipment manufacturing | | |
| | Conveyor & conveying equipment manufacturing | | |
| | Overhead traveling crane, hoist, & monorail system manufacturing | | |
| | Packaging machinery manufacturing | | |
| | all other miscellaneous general purpose machinery manufacturing (part | | |
| | Radio & television broadcasting & wireless communications equipment manufacturing | | |
| | Audio & video equipment manufacturing | | |
| | Semiconductor & related device manufacturing | | |
| | Printed circuit assembly (electronic assembly) manufacturing | | |
| | Other electronic component manufacturing | | |
| | Watch, clock, & part manufacturing | | |
| | Other measuring & controlling device manufacturing | | |
| | Relay & industrial control manufacturing | | |
| | Motor vehicle seating & interior trim manufacturing | | |
| | All other motor vehicle parts manufacturing | | |
| | Railroad rolling stock manufacturing | | |
| | Ship building & repairing | | |
| | Institutional furniture manufacturing | | |
| | Showcase, partition, shelving, & locker manufacturing | | |
| | Jewelry (except costume) manufacturing | | |
| | Silverware & holloware manufacturing | | |
| | Costume jewelry & novelty manufacturing | | |
| | Doll & stuffed toy manufacturing | | |
| | Electrical apparatus & equipment, wiring supplies, & related equipment merchant wholesalers | | |
| | Recyclable material merchant wholesalers | | |
| | Business to business electronic markets | | |
| | Wholesale trade agents & brokers | | |
| | Other building material dealers | | |

(*Continued*)

**Table 5.** (*Continued*)

| Industry Category | Industries by NAICS Codes with Potential Beryllium Exposure ⩾ 0.1 μg/m³* NAICS Industry Description | Examples of Jobs with Potential Beryllium Exposure within the Industry Category† | Related Products Possibly Containing Beryllium within the Industry Category (Partial Listing) |
|---|---|---|---|
| | Other support activities for water transportation | | |
| Defense | Military armored vehicle, tank, & tank component manufacturing | Nuclear weapons worker | Avionics packaging |
| | | Prep shop | Electrical insulators in power amplifier tubes & radars |
| | | | Heat shields |
| | | | Heat sinks on missiles, space vehicles, & satellites |
| | | | Mast-mounted sights |
| | | | Mirror support structures |
| | | | Missile guidance systems |
| | | | Nuclear weapon components |
| | | | Submarine hatch springs |
| | | | Tank mirrors |
| Construction | New multifamily housing construction (except operative builders) | Abatement tech | Abrasive blasting media made from coal or copper slag |
| | Residential remodelers | Abrasive blaster | |
| | Industrial building construction | Blaster | |
| | Commercial & institutional building construction | Burner | |
| | Water & sewer line & related structures construction | Carpenter | |
| | Oil & gas pipeline & related structures construction | Cutter | |
| | Power & communication line & related structures construction | Deleading operator | |
| | Highway, street, & bridge construction | Electrician | |
| | Other heavy & civil engineering construction | Insulator | |
| | Structural steel & precast concrete contractors | Laborer | |
| | Glass & glazing contractors | Lead man | |
| | Other foundation, structure, & building exterior contractors | Operator | |
| | Electrical contractors | Painter blaster | |
| | Plumbing, heating, & air-conditioning contractors | Sandblaster | |
| | Paint & wall covering contractors | Slater | |
| | Site preparation contractors | Welder | |
| Energy & electrical | Hydroelectric power generation | Electrician | Circuit breaker parts<br>Coal slag |
| | Fossil fuel electric power generation | | Electrical contacts, switches, & fuse clips |
| | Nuclear electric power generation | | Heat exchanger tubes |
| | Other electric power generation | | High voltage electrical components |
| | Electric bulk power transmission & control | | Microelectronics |
| | Electric power distribution | | Microwave devices |
| | | | Nuclear reactor components |
| | | | Oil field drilling & exploring devices |
| | | | Relays & switches |
| Transportation & public utilities | Line-haul railroads | Blaster | Abrasive blasting media made from coal or copper slag |

*(Continued)*

**Table 5.** (*Continued*)

| Industry Category | Industries by NAICS Codes with Potential Beryllium Exposure ⩾ 0.1 μg/m³* NAICS Industry Description | Examples of Jobs with Potential Beryllium Exposure within the Industry Category† | Related Products Possibly Containing Beryllium within the Industry Category (Partial Listing) |
|---|---|---|---|
| | School & employee bus transportation | Mechanic | |
| | Other support activities for road transportation | Painter | |
| | Hazardous waste treatment & disposal | | |
| | Solid waste landfill | | |
| | Solid waste combustors & incinerators | | |
| | Other nonhazardous waste treatment & disposal | | |
| | Materials recovery facilities | | |
| Miscellaneous | Support activities for animal production | Artist | Copper-beryllium alloys |
| | Plumbing, heating, & air-conditioning contractors | (e.g. sculptor using beryllium alloys) | |
| | All other home furnishings stores | Electron gun operator | |
| | Hardware stores | Sandblaster | |
| | Outdoor power equipment stores | Welder | |
| | Sporting goods stores | | |
| | Other support activities for water transportation | | |
| | Research & development in the physical, engineering, & life sciences | | |
| | Locksmiths | | |
| | Other services to buildings & dwellings | | |
| | Septic tank & related services | | |
| | All other miscellaneous waste management services | | |
| | Independent artists, writers, & performers | | |
| | Consumer electronics repair & maintenance | | |
| | Computer & office machine repair & maintenance | | |
| | Other electronic & precision equipment repair & maintenance | | |
| | Commercial & industrial machinery & equipment (except automotive & electronic) repair & maintenance | | |
| | Home & garden equipment repair & maintenance | | |
| | Appliance repair & maintenance | | |
| | Footwear & leather goods repair | | |
| | Other personal & household goods repair & maintenance | | |

*Definition of abbreviations*: MIG = metal inert gas; NAICS = North American Industry Classification System; NC = numerical control; SX = wire gun; TIG = tungsten inert gas.

NAICS Industry Classification Lists are derived from publications demonstrating where sampling has indicated the presence of beryllium. These lists are not comprehensive but are intended to illustrate the variety of industries and workplaces where beryllium might be found. Data in this table are from References 2, 35, 87, and 153–158.

*NAICS codes were converted from Standard Industrial Classification codes using the Correspondence Tables at http://www.census.gov/eos/www/naics/.

†Potential jobs at risk do not include bystander exposure hazards, such as clerical staff and security personnel, in whom exposure has also been documented.

though wage and job loss can occur when a worker with BeS is medically precluded from further exposure to beryllium (118).

Individuals with BeS who worked for contractors or subcontractors at DOE facilities or other covered beryllium vendor are eligible for medical monitoring under the federal program administered by the DOL (121).

### Natural History and Management of CBD

The natural history of CBD is variable (54, 57, 117, 123, 124, 126, 128, 143, 144). Asymptomatic cases of CBD are being detected due to the use of the BeLPT in medical surveillance, with some patients remaining stable and symptom-free after diagnosis and others developing clinically significant disease. Patients with CBD demonstrate lung function decline at a greater rate than individuals with BeS on average (143). Among patients with clinically significant disease, most experience a gradual downhill course, and spontaneous reversal is rare (123, 128, 145). Although the clinical course of CBD detected by surveillance and risk factors for progression both need further investigation, being a machinist was associated with a greater rate of decline in lung function and gas exchange in one study (143). There is a paucity of evidence that removal from exposure results in improvement (146).

Patients with CBD are followed on at least an annual basis, with the frequency dictated by the severity of disease and the need for treatment. Those who require pharmacological therapy are seen more frequently. Attempts to remove beryllium with chelating agents have been unsuccessful (147), probably because most forms of beryllium are poorly soluble and persist in the body for the lifetime of the individual (126). Thus, medical therapy of CBD is directed at suppressing the immune response to beryllium and subsequent granuloma formation and fibrosis. Systemic corticosteroids are considered first-line therapy. Randomized trials of corticosteroids have never been performed, but observational evidence suggests that treatment of clinically apparent CBD (10, 96, 123, 146–149) is associated with improved pulmonary function, radiographic abnormalities, respiratory symptoms, and functional status.

The decision to initiate systemic corticosteroids in patients with CBD is based on the combination of pulmonary symptoms and physiologic findings, not chest imaging. Therapy is usually initiated when there is evidence of significant lung function decline or abnormality. Prednisone is started at 20 to 40 mg daily or every other day for 3 to 6 months to achieve maximum improvement of pulmonary function. The dosage is gradually reduced using PFT to assess for evidence of relapse. Relapse is common and is managed by increasing the dose to the level that stabilized or improved pulmonary function. Lifetime treatment with corticosteroids is often necessary, but a dose reduction is tried every 2 to 3 years. A steroid-sparing therapy is considered if significant side effects are experienced (e.g., methotrexate, azathioprine, cyclophosphamide, CellCept, and infliximab). This approach is based on the treatment approach for sarcoidosis given clinical, histopathologic, and radiographic similarities of the diseases, as well as paucity of direct evidence for the treatment of CBD (138).

Supportive and preventive therapies are administered as needed, similar to the management of other types of interstitial lung disease. Lung transplantation has been used in a few patients with end-stage CBD, but its effectiveness is unknown. Workers' compensation programs typically recognize CBD as a compensable occupational illness. Patients with CBD who worked for contractors or subcontractors at DOE facilities or other covered beryllium vendor are eligible for compensation under the federal program administered by the DOL (121).

## Prevention

Opportunities for control of exposure to beryllium should be considered in any facility that uses beryllium-containing products (1). The goals of a control program are to limit inhalation and dermal exposures as much as possible and reduce the number of employees who are directly or indirectly exposed. This may be achieved (in descending order of effectiveness) by elimination or substitution, engineering controls (e.g., process confinement, local ventilation), personal protective equipment, and administrative changes such as exclusion of workers from specific areas to prevent nonessential contact with beryllium. Recent work that resulted from a collaboration of NIOSH with the primary U.S. producer of beryllium products suggests that a rigorous and comprehensive approach to workplace control of exposure to beryllium can successfully reduce the incidence of BeS (48–50). Studies were conducted at three beryllium production facilities that compared rates of BeS for workers hired during similar periods of time before and after implementation of a comprehensive preventive program that included increased respiratory and dermal protection, limiting migration of beryllium away from the work process, attention to housekeeping, and education of workers and management (150). At a beryllium oxide ceramics manufacturing facility, a significant reduction in BeS was observed in workers hired after program implementation (48). At a copper-beryllium finishing plant, fewer workers became sensitized after implementation of a preventive program, although conclusions about the program's efficacy are limited by imprecision due to the facility's small workforce (49). Finally, at a large beryllium metal, oxide, and alloy production plant, a study also showed evidence of a reduction of risk of sensitization after implementation of the company's preventive program (50). If BeS can be prevented or reduced, then it is reasonable to expect that CBD might also be prevented or reduced.

Reduction of exposure concentration is unlikely to prevent all cases of BeS or CBD (53). Medical surveillance in workplaces that use beryllium-containing materials can identify workers with BeS so that they can be evaluated for CBD and then managed as described above. The BeLPT is the cornerstone of medical surveillance of beryllium-exposed workers (1). Individuals with beryllium exposure who do not have BeS at the time of initial evaluation generally undergo periodic BeLPTs because they remain at future risk.

The DOE medical surveillance program provides an example of medical surveillance. The DOE provides screening based on an individual's exposure history and potential disease risk (151). Workers regularly employed in activities that involve exposure to beryllium are most at risk and are offered annual screening. Workers at a DOE facility who have been previously exposed to airborne concentrations of beryllium are offered screening every 3 years. The performance of the BeLPT in the DOE medical surveillance program supports its use in screening for BeS in populations with a high prevalence of BeS (107, 111, 112, 118), although its usefulness in populations with low prevalence of BeS is uncertain (152).

Additional benefits of medical surveillance include defining at-risk groups, identifying hazardous jobs and processes, and prioritizing efforts to reduce inhalational and dermal exposures. Prevalence and incidence of BeS may be examined by risk factors such as job, task, or area by questionnaire or linking to administrative data. If process- and exposure-related risks identified by surveillance are linked to preventive actions that reduce exposures, such as additional exposure controls, it is reasonable to expect that BeS and CBD may be reduced or prevented.

Preventive efforts do not have to wait until BeS or CBD is identified. Interventions can be directed at preventing cases through a comprehensive approach to improved control of exposures. Environmental monitoring data, if available, can be used to target areas and processes for interventions.

## Conclusions

Beryllium continues to have a wide range of industrial applications; as a result, many workers are exposed throughout the world, and BeS and CBD continue to occur. A diagnosis of BeS is based on two abnormal BeLPTs or the combination of one abnormal and one borderline BeLPT. A diagnosis of CBD requires evidence of both a specific immune response to beryllium and granulomatous inflammation in lung tissue.

Ongoing monitoring of patients with confirmed BeS and CBD is necessary because BeS can progress to CBD, and mild CBD can progress to more severe disease. This includes symptom review, physical examination, and PFT. Patients with significant lung function decline are usually treated with systemic corticosteroids in a manner similar to that used for sarcoidosis, even though no randomized trials of such therapy for CBD have been published.

Control of exposure to beryllium appears to reduce the incidence of BeS (48–50). However, the reduction of exposure alone is probably insufficient to prevent all cases of BeS or CBD, thereby providing an additional need for medical surveillance. Medical surveillance with the BeLPT can identify workers with BeS so that they can be evaluated for CBD and managed accordingly. It can also identify higher-risk jobs/processes, which may facilitate the prioritization of prevention efforts and subsequent evaluation of the effectiveness of these efforts in decreasing the risk of BeS. If BeS can be reduced, then CBD might also be reduced, along with CBD-related impairment and disability. ■

This official statement was prepared by an *ad hoc* subcommittee of the Environmental, Occupational, and Population Health Assembly.

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**Author Disclosures:** J.R.B. reported serving on the California Air Resources Board of the California Environmental Protection Agency ($100,000–249,999) and on an advisory committee of the U.S. Environmental Protection Agency. J.L.A. reported serving as a consultant pathologist and expert witness for various law firms and physicians in cases of known or suspected occupational/environmental lung and other diseases ($50,000–99,000). L.A.M. reported receipt of research support from the U.S. Department of Energy-Hanford ($250,000 or more), Beryllium Biobank ($250,000 or more), Centocor ($25,000–99,999), and Mondo Biotech ($10,000–50,000), service as an expert witness for Golub and Honik (<$1,000), and employment by National Jewish Health involving patients with occupational lung diseases and interpretation of BeLPTs. J.M.-Q. reported consulting for Mondo Biotech ($1,001–5,000), lecture fees from Boehringer Ingelheim ($1,001–5,000) and Talecris ($1,001–5,000), a research grant from German Federal Research ($100,000 or more), and a co-held patent for blockade of CC18 signaling via CCR6 as a therapeutic option in fibrotic diseases and cancer. G.O. reported serving as medical director of the smoking cessation clinic of the Montreal Chest Institute of McGill University Health Centre. L.D.P. reported a research grant from the U.S. Department of Energy. C.S. reported lecture fees from Abbott, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Pfizer ($1,001–5,000 each). C.R.S. reported employment as an epidemiologist by the National Institute of Occupational Safety and Health. P.F.W. reported employment as an industrial hygienist by the U.S. Department of Energy. R.A.D., E.F., A.P.F., and T.K.T. reported that they had no financial interests relevant to document subject matter.

**EDITOR'S NOTE:** This document is a Clinical Statement and not a Clinical Practice Guideline, meaning that evidence-based recommendations for patient care are not provided and are beyond the scope of the document. The goal of a Statement is to discuss relevant evidence and may describe how the expert coauthors apply the evidence in their clinical practices.

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