

Systematic review: progression of beryllium sensitization to chronic beryllium disease

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Background	The relevance of beryllium sensitization testing for occupational health practice and prevention is unclear.
Aims	To analyse the natural course of beryllium sensitization and clarify the prognosis following cessation of exposure among sensitized workers.
Methods	An electronic literature search was conducted in PubMed, Embase, Toxline and Cochrane databases supplemented by a manual search. Data abstraction and study quality assessment with adapted guideline checklists were performed independently by three reviewers. Seven studies met the eligibility criteria and were included in the systematic review; however, six of the seven studies were of low methodological quality.
Results	A substantial (although not specifically quantifiable) proportion of beryllium-sensitized employees will develop chronic beryllium disease (CBD). To date, it is unknown if cessation of exposure in sensitized workers reduces the progression rate to CBD.
Conclusions	To determine the utility of regular assessments for beryllium sensitization among exposed workers, there is a need for prospective studies. This should include detailed and continuous exposure monitoring, regular tests for beryllium sensitization and a thorough diagnostic evaluation of sensitized workers to confirm or exclude CBD.
Key words	Beryllium lymphocyte proliferation test; beryllium sensitization; chronic beryllium disease; exposure cessation; occupational health practice; systematic review.

Introduction

Beryllium and beryllium-containing alloys are used in different industries worldwide, particularly in the atomic energy and defence, space, aeronautics, computer and electronics industries. Grinders, machinists, hot press operators, welders and dental technicians may come into contact with respirable beryllium or its compounds in the course of their work. Müller-Quernheim *et al.* [1] reported that increasing amounts of beryllium and its alloys are imported in Germany, thus increasing occupational exposure, which may lead to chronic beryllium disease (CBD). Affected workers present with

non-productive cough, dyspnoea on exertion and sometimes fever. Pulmonary function tests reveal a restrictive pattern, and chest X-rays or computed tomography (CT) scans show reticular-nodular infiltrates, which consist of non-necrotizing granulomatous lesions in histology [2].

In Germany, CBD is a recognized occupational disease (no. 1110). However, claims are low ($n = 21$ in 2007–09) [3]. As CBD is very similar to the more frequently diagnosed sarcoidosis (estimated incidence in Germany 10–12/100 000 per year) [4], it is assumed that many cases are misdiagnosed as sarcoidosis. In an in-depth examination of patients diagnosed with sarcoidosis, Müller-Quernheim *et al.* [5] found that a large

number of patients (34 out of 84) who were exposed to beryllium suffered from CBD. It is, therefore, hypothesized that a large number of CBD cases are unreported.

Since the late 1980s, sensitization to beryllium can be detected with the beryllium lymphocyte proliferation test (BeLPT) [6]. In the BeLPT, mononuclear cells derived from peripheral blood or fluid from bronchoalveolar lavage (BAL) are challenged with beryllium salts *in vitro*. A response is considered positive if beryllium induces proliferation of sensitized lymphocytes [7]. To decide whether BeLPT is useful as a routine diagnostic tool in occupational health surveillance, there is a need for evidence that preventive or therapeutic measures (as a consequence of a positive BeLPT) improve the prognosis of sensitized employees. This systematic review specifically focuses on the effects of preventive measures (cessation of exposure) on the prognosis of beryllium-sensitized employees. The systematic review was, therefore, conducted to clarify (i) the natural course of beryllium sensitization and (ii) the prognostic relevance of cessation of exposure among sensitized workers. It was hypothesized that exposure cessation in newly beryllium-sensitized persons reduces the risk of CBD development.

Methods

This systematic review is part of the ongoing development of an evidence-based German guideline of 'Preventive occupational medical care for chronic beryllium diseases'. This guideline development started in July 2007. A detailed report is available from the authors, providing a description of the methods used. Ethical approval was not required for our study as our systematic review did not include any primary data. The guideline development is based on nine *a priori*-defined key questions; two key questions are the topic of this systematic review:

- (i) What is the risk of beryllium-sensitized persons developing CBD?
- (ii) Is the risk of acquiring CBD higher among beryllium-sensitized workers with ongoing beryllium exposure than among beryllium-sensitized workers whose beryllium exposure has ceased?

This systematic review was performed in accordance with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement [8].

A systematic electronic literature search was done using PubMed (1950 to 19 March 2010), Embase (1989 to 8 April 2008), Toxline (from inception until 9 May 2008) and Cochrane (from inception until 16 April 2008) databases. The search term 'beryllium' OR 'berylliosis' was used. The systematic electronic search was limited to original articles reporting on humans and having an abstract, but it did not apply any language constraints. All randomized controlled trials (RCT), systematic reviews of RCT or cohort studies and cohort

studies or cross-sectional studies giving basic information about temporal course were included.

Initially, titles and abstracts of the studies were screened by two independent scientists to eliminate studies that were unrelated to the *a priori*-defined research questions. The included papers were assigned to the specific research questions. Subsequently, the full texts of the remaining studies were thoroughly and independently examined by three reviewers to determine if the inclusion criteria were met. The eligibility criteria were specified as follows:

- (i) Population: all humans (key question 1), respectively beryllium-sensitized employees (key question 2)
- (ii) Intervention: not applicable (key question 1), occupational beryllium exposure (key question 2)
- (iii) Outcome: CBD (key questions 1 and 2).

At this stage, the exclusion of studies was conducted by telephone conferences; the reasons for exclusions (improper study design, e.g. narrative review or cross-sectional study without information about temporal course, lack of beryllium-sensitized study population and lack of CBD diagnosis as outcome) were documented for each paper. Workers with simultaneous diagnosis of beryllium sensitization and CBD would not have contributed to the analysis of prognosis of beryllium sensitization. Therefore, only studies giving the results of follow-up examinations for workers free of CBD at the time of beryllium sensitization diagnosis were included.

Data abstraction from the included articles and study quality assessment were done independently by three reviewers (A.S., S.L., D.G.) and discussed in three telephone conferences. The data abstraction form included information on relevant study characteristics such as study design, study region, source population, number of participants, participant characteristics (age, sex), occupational beryllium exposure after the diagnosis of beryllium sensitization, potential misclassification of exposure, duration of follow-up, outcomes, potential misclassification of outcomes and funding. The mentioned study characteristics of the relevant studies were entered into evidence tables (Table 1).

The studies were examined according to a combination of the criteria described by Scottish Intercollegiate Guidelines Network (SIGN) [9] and Critical Appraisal Skills Programme [10] (see the checklist available as Supplementary data at *Occupational Medicine* Online). Considering the internal/external validity, three reviewers independently and systematically assessed the studies on a three-level scale (+++, +, -) according to SIGN (see Table 2) [9] and documented their results in an appraisal form. Studies were classified as of low methodological quality (SIGN-) when methodological weaknesses were believed to considerably influence the core results. The results of the critical appraisal were compared and discussed in three telephone conferences, leading to a consensus in all cases where opinions diverged.

Table 1. Studies concerning the natural course of beryllium sensitization and predictors of progression to CBD

First author, publication year/ Study region/ Time of baseline examination	Study design/ Follow-up (mean, range)	Population		Exposure	Outcome at follow-up examination	Results (1. Natural course after Be-sensitization, 2. Predictors of progression to CBD)
		Industry; number of companies	No. of subjects, definition of Be-sensitization at baseline			
Duggal, 2010 [12] USA (various sites) 1992–2001	Cohort study 7.1 years (SD = 3.0 years)	Single beryllium manufacturer with plants in Elmore, Ohio, Reading, Pennsylvania, Tucson, Arizona	50 Be-sensitized persons ^a ; mean age 44.2 years, 78 males)	Questionnaire-based: mean Be exposure 15.6 years; time since exposure termination	Clinical abnormality consistent with CBD: X-ray changes and/or FVC <80% predicted and/or DLCO <80% predicted and or treatment with oral steroids for CBD	1. 2% of Be-sensitized (<i>n</i> = 1) develop clinical abnormality consistent with CBD 2. (single) patient with clinical abnormality consistent with CBD was Be-exposed after Be-sensitization; exposure status of 49 Be-sensitization persons after diagnosis of sensitization unknown
Kreiss, 1993 [14] Denver, Colorado 1987–90	Cross-sectional ^b 1.8 years	Nuclear workers (<i>n</i> = 1 plant) plus (few) volunteers	6 Be-sensitized workers ^a aged 33–61 years	Not applicable for research question no. 1. (as natural course of beryllium sensitization is considered)	CBD with granulomas	1. 3 of 6 Be-sensitized develop CBD
Mroz, 2009 [13] Denver, Colorado 1982–2002	Cohort study Unknown (max. 20 years)	Unknown (study population: all individuals clinically evaluated at the National Jewish Medical and Research Center)	229 Be-sensitized workers ^a aged 52 years (117 males, 52 females)	Not applicable for research question no. 1.	CBD: BeLPT ^b and granuloma or mononuclear cell infiltrates in lung biopsy	1. 8.8% (22 of 229 Be-sensitized) develop CBD
Newman, 1996 [15] Denver, Colorado 1986–?	Cross-sectional ^b >5 years (for <i>n</i> = 6 persons)	Unknown (study population: recruitment by National Jewish Center for Immunology and Respiratory Medicine)	22 Be-sensitized persons ^a ; of these 6 persons with CBD follow-up >5 years; age range for Be-sensitized unknown	Not applicable for research question no. 1.	CBD: abnormal clinical findings, increasingly lymphocytic lavage and noncaseating granulomas on lung biopsy	1. 3 of 6 Be-sensitized develop CBD
Newman, 2001 [16] Alabama 1995	Cross-sectional ^b <2 years	Beryllium machining plant (<i>n</i> = 1), median machining exposures of 0.3 µg/m ³	5 Be-sensitized persons ^a of 187 employees; mean age of screened employees 39 years, 90% males	Not applicable for research question no. 1.	CBD with granuloma and/or mononuclear cell infiltrates in lung tissue; 'probable CBD': BAL-lymphocytosis and BeLPT ^b	1. 4 of 5 Be-sensitized develop CBD
Newman, 2005 [11] Denver, Colorado 1988–98	Cohort study 3.8 years (1.0–9.5 years)	Unknown (study population: all individuals clinically evaluated at the National Jewish Medical and Research Center)	55 Be-sensitized persons ^a with bronchoscopic follow-up; altogether 76 Be-sensitized persons (66 males, 10 females) aged 52.9 (31–80) years at baseline)	At time of CBD diagnosis 35.3% Be-exposed (versus 29.0% of Be-sensitized without CBD); 44.2% of CBD patients are machinist (versus 16.2% of Be-sensitized without CBD)	CBD with granulomas and/or mononuclear cell infiltrates in lung tissue	1. 31% of Be-sensitized (<i>n</i> = 17) develop CBD (progression rate = 6–8%/year) 2. CBD risk (OR) for machinists = 4.4 (95% CI 1.07–17.8)

(Continued)

Table 1. (Continued)

First author, publication year/ Study region/ Time of baseline examination	Study design/ Follow-up (mean, range)	Population		Exposure	Outcome at follow-up examination	Results (1. Natural course after Be-sensitization, 2. Predictors of progression to CBD)
		Industry; number of companies	No. of subjects, definition of Be-sensitization at baseline			
Rom, 1983 [17] Delta, Utah 1979	Cross-sectional ^b 3 years	Surface mine and process mill (beryllium production)	13 Be-sensitized (1 abnormal BeLPT) male persons (of 82 participating employees), response unknown, mean age 38.8 years	Not applicable for research question no. 1.	'CBD' diagnosis: lung function, thoracic X-ray	1. 0 of 13 Be-sensitized develop 'CBD'

Be, beryllium; CBD, chronic beryllium disease; BeLPT, beryllium lymphocyte proliferation test; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; BAL, bronchoalveolar lavage.

^a≥2 abnormal BeLPT tests with no evidence of CBD at baseline (no granulomas and/or mononuclear cell infiltrates on transbronchial lung biopsy).

^bCross-sectional with basic information on temporal course.

^c≥2 abnormal BeLPT tests with no evidence of CBD in clinical examination including blood and BAL fluid markers.

Table 2. Study evaluation criteria according to SIGN [9]

Code	How well was the study done to minimize the risk of bias or confounding and to establish a causal relationship between exposure and effect?
++	'All or most' of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought 'very unlikely' to alter.
+	'Some' of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought 'unlikely' to alter the conclusions.
-	'Few or no' criteria fulfilled. The conclusions of the study are thought 'likely or very likely' to alter.

Results

In total, 5847 citations yielded by the electronic search were reviewed, with 5196 articles being excluded after title and abstract screening, and 136 of the remaining 651 articles were assigned to the two research questions of this systematic review. Of these, 129 articles were excluded after full-text review since they did not meet the eligibility criteria, leaving a total of seven studies included in the systematic review (Figure 1). All of the seven studies dealt with the first research question, but only two of them dealt with the second research question.

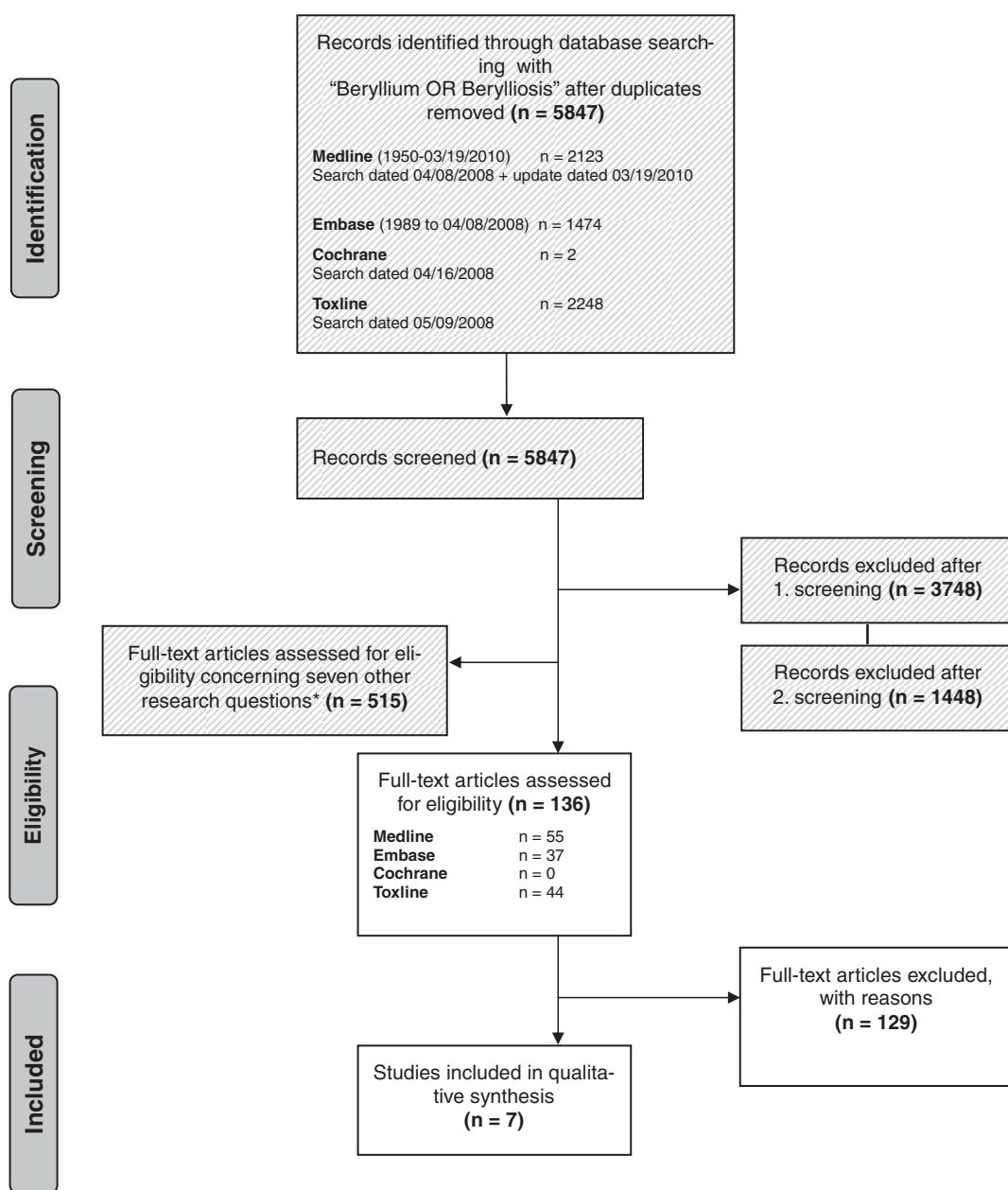
The characteristics of the three cohort studies [11–13] and four cross-sectional studies with basic information about temporal course [14–17] are summarized in Table 1. The results of these studies are presented separately for research questions 1 and 2.

In response to the first research question (What is the risk of beryllium-sensitized persons developing CBD?), six of the studies were of insufficient methodological

quality [12–17]. In this review, only subjects without CBD diagnosis at the time of beryllium sensitization diagnosis were considered further, and subjects with simultaneous beryllium sensitization diagnosis and CBD diagnosis were excluded.

The studies published by Kreiss *et al.* [14] and Newman *et al.* [15] provided information about the clinical course for under-10 beryllium-sensitized persons. As there was considerable overlap between the study populations of these studies, with Newman *et al.*'s study population being larger [11], the clinical course of beryllium sensitization could not be derived from these studies.

In a study of Mroz *et al.* [13], 22 out of 229 beryllium-sensitized persons (9%) acquired a new CBD during a 10-year interval (1992–2002). Again there was considerable overlap with the Newman *et al.*'s study population [11]. Moreover, the authors did not give the mean time of follow-up. In a surveillance study of workers in a beryllium machining plant [16], four of five sensitized workers developed a CBD within a short time interval



*Will be published separately

Figure 1. Literature search according to PRISMA flow diagram [9].

of less than 2 years. Rom *et al.* [17] did not identify any of the 13 beryllium-sensitized workers who developed radiographic changes consistent with CBD over a period of about 3 years. Duggal *et al.* [12] observed 50 beryllium-sensitized employees of a beryllium manufacturer (mean duration of beryllium exposure 15.6 years) for a mean follow-up time of about 7 years. At the time of the baseline examination, these beryllium-sensitized subjects had at least two abnormal BeLPT tests and no evidence of granulomas and/or mononuclear cell infiltrates on transbronchial lung biopsy. In this study, only 1 out of

the 50 beryllium-sensitized employees developed a clinical manifestation of CBD [12]. However, histological diagnosis was lacking for these 50 subjects. Moreover, the response rate (40%) was low. The only study with an acceptable study quality with respect to the first research question included 55 sensitized persons [11]. At the time of the baseline examination, these beryllium-sensitized subjects had at least two abnormal BeLPT tests with no evidence of granulomas and/or mononuclear cell infiltrates on transbronchial lung biopsy. More than 80% of these beryllium-sensitized persons were employed in

the nuclear weapons industry. At the time of baseline evaluation, the mean period of beryllium exposure was 13.5 years among subjects later progressing to CBD and 11.2 years among subjects later not progressing to CBD. Applying bronchoscopic follow-up examinations, 31% ($n = 17$) developed a new CBD during a mean follow-up time of 3.8 years. The authors determined a CBD progression rate of about 6–8% per year after initial diagnosis of beryllium sensitization. As a methodological limitation of this study, a well-defined study base is lacking. All beryllium-sensitized persons who were clinically evaluated at the National Jewish Medical and Research Center in Denver, CO, were included. Therefore, potential selection bias limits the generalizability of the study results for any specific group of workers. Despite the considerable inconsistencies among the corresponding studies, as a kind of ‘best-estimate’ we nevertheless assumed a yearly progression rate of 6–8% from beryllium sensitization to CBD among beryllium-sensitized persons.

With regard to research question 2 (Is the risk of CBD higher among beryllium-sensitized workers with ongoing beryllium exposure than among beryllium-sensitized workers whose beryllium exposure is ceased?), only two studies gave rudimentary information about the exposure status following the diagnosis of beryllium sensitization [11,12]. Both studies, including Newman *et al.*'s study [11] (which was of an acceptable quality with respect to the first research question), were of insufficient methodological quality (mainly due to the unknown temporal course of beryllium exposure). In the study published by Duggal *et al.* [12], the only beryllium-sensitized worker who developed clinical CBD during follow-up was still exposed to beryllium at the time of CBD diagnosis. For the other 49 workers (staying ‘healthy’), the proportion of workers with continued beryllium exposure after the diagnosis of beryllium sensitization was not reported in this paper [12]. According to M. Cullen (personal communication), the senior author of the publication of Duggal *et al.* [12], about two-thirds of employees left exposure after being diagnosed as beryllium sensitized.

In Newman *et al.*'s study [11], the proportion of individuals with current beryllium exposure at the time of CBD diagnosis (35%) did not significantly differ from the corresponding proportion among individuals who remained beryllium sensitized (29%). Interestingly, 2 of the 17 individuals who progressed to CBD had only incidental or bystander exposure. Information about the course of exposure for the whole time interval between beryllium sensitization and CBD incidence is missing. The elevated CBD risk among sensitized workers in machining beryllium (OR = 4.4; 95% CI 1.07–17.8) did not indicate an adverse effect of beryllium exposure after diagnosis of beryllium sensitization, as no differentiation between elevated sensitization risk and elevated progression risk after sensitization was made by Newman *et al.* [11].

Discussion

In this systematic review, we found that a substantial proportion of beryllium-sensitized employees were going to develop CBD. Nevertheless on the basis of our systematic review, to date it remains unclear if exposure cessation as a consequence of diagnosis of beryllium sensitization reduces the progression rate to CBD.

This systematic review focuses on the use of BeLPT for secondary prevention of CBD in sensitized workers but not on its use for the evaluation of primary prevention programmes. Several surveillance programmes [7,18] reported that lymphocyte proliferation testing might help to identify high-risk areas and high-risk processes (e.g. machining) and evaluate the effect of specific preventive measures (e.g. preventive programmes including dermal protection). Independent from primary preventive considerations, the present question of a potential individual benefit of BeLPT is crucial to decide whether testing is useful as routine diagnostic tool in occupational health surveillance.

However, in our very sensitive and comprehensive search, we found that only a few studies helped to answer the two research questions. Moreover, the results of these few studies were inconsistent; for example, one study (methodologically inadequate) found that only 1 out of 50 beryllium-sensitized workers developed CBD within 7 years [12], and another study (methodologically acceptable) found that 17 of 55 beryllium-sensitized persons developed CBD within an even shorter time interval of about 4 years [11]. This obvious discrepancy in the progression from beryllium sensitization to incident CBD might be explained by differences in outcome definitions; Newman *et al.* [11] based the CBD diagnosis on evidence of granulomas and/or mononuclear cell infiltrates in lung tissue, whereas Duggal *et al.* [12] used clinical criteria (changes in chest X-ray or lung function). The latter—exclusively clinical outcome definition—appears to be an insensitive method of CBD diagnosis, leading to potential underestimation of progression rates.

As six of the seven studies that deal with the two research questions are of insufficient quality, methodological weaknesses (*inter alia* inadequate diagnostic procedures) might at least partly explain the inconsistent results. As an alternative explanation, the progression rate might depend on the intensity of beryllium exposure varying between the single studies. However, due to lack of studies investigating progression, this explanation remains speculative. Moreover, M. Cullen (personal communication) suspects that workers at the production facilities studied by Duggal *et al.* [12] had (at least in their early careers) on average much higher exposures than those studied by Newman *et al.* [11]. Finally, in some plants, beryllium-sensitized workers might continue working in a beryllium-exposed environment, whereas in other plants they might be moved to non-exposed

workplaces. This might at least partly explain the differing progression rates to CBD within plants.

Two recently published case-control studies point to potential differences in the risks for beryllium sensitization and risks for CBD [19,20]: CBD but not beryllium sensitization might be associated with cumulative beryllium exposure. It can be concluded from the cited studies that the effect of exposure cessation subsequent to the diagnosis of beryllium sensitization might depend on the cumulative beryllium exposure at time of sensitization diagnosis. However, as case-control studies do not allow firm conclusions about the individual course from beryllium sensitization to development of CBD, they were not included in this systematic review.

Although the toxicity of beryllium has been known for decades [21], the body of evidence available to answer our research questions was limited, which demonstrates a lack of research efforts to answer crucial questions about occupational safety in beryllium-exposed workplaces. The available evidence is insufficient to recommend regular tests for beryllium sensitization for secondary preventive purposes. In their discussion of the usefulness of BeLPT for screening of asymptomatic individuals, Borak *et al.* [22] point to the lack of information about the likelihood and probable magnitude of benefits and harms to screened persons. However, these authors do not base their conclusion on a systematic review, and they do not take into consideration the potential harmful effect of continued beryllium exposure after beryllium sensitization. Nevertheless on the basis of our systematic review, to date it is unknown if exposure cessation as a consequence of diagnosis of beryllium sensitization reduces the progression rate to CBD. As RCT on exposure cessation would be unethical and practically unfeasible, there is a need for observational, prospective studies among beryllium-exposed workers, including detailed and continuous exposure monitoring, regular tests for beryllium sensitization employing peripheral blood and/or BAL mononuclear cells and regular clinical and radiographic examination of beryllium-sensitized persons. In case of nodular infiltrates chest X-ray or CT scan compatible with CBD, an additional bronchoscopy to obtain transbronchial biopsies for the demonstration of non-necrotizing granulomata needs to be discussed. There are several challenges of conducting systematic longitudinal follow-up of individuals who are asymptomatic: the need for high participation rates limits the possibility to conduct regular bronchoscopic examinations of asymptomatic individuals in short-term intervals; a multicentre approach should be chosen to allow firm conclusions against the background of regional variation in regulatory frameworks. We nevertheless would like to express the urgent need for prospective studies among beryllium-exposed workers to allow an evidence-based decision about the usefulness of regular tests for beryllium sensitization.

Key points

- Chronic beryllium disease is clinically and histologically indistinguishable from the more frequently diagnosed sarcoidosis and therefore many cases may be misdiagnosed as sarcoidosis.
- Since the late 1980s, sensitization to beryllium—a cell-mediated immune response—can be detected with the beryllium lymphocyte proliferation test.
- To date, published studies do not allow reliable recommendations on prognostic benefits of detection of beryllium sensitization in healthy exposed employees/individuals.

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Conflicts of interest

The authors declare that they have no competing interests.

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