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Beryllium

A review of the health effects and the evidence for screening or surveillance in workers exposed to beryllium

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A review of the health effects and the evidence for screening or surveillance in workers exposed to beryllium

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There are however an emerging number of cases of subclinical disease and beryllium sensitization (BeS) that are being detected with new immunological tests, namely the beryllium lymphocyte proliferation test (BeLPT). Almost all the recent data on screening beryllium workers relates to the BeLPT, and more traditional screening programmes such as spirometry and chest x-rays that have been in use since the 1950s have only been evaluated as secondary endpoints.

Whilst the BeLPT has revolutionised the diagnosis of chronic beryllium disease (CBD), concerns have been raised about its inter- and intra-laboratory variability, possible reversibility in patients and uncertain sensitivity and specificity. There is also debate about the natural history of BeS and subclinical CBD and the ethical aspects of identifying disease early when there is no treatment, and subsequent employment implications. Another issue for the UK is the fact that only one laboratory offers BeLPT testing, although certain evidence supports double sampling of tests across laboratories to improve sensitivity and specificity. All these factors have led to certain US based groups advocating the use of BeLPT for screening and others not.

Therefore, in the US, a definitive stance on the content of a health surveillance programme has not been possible from the current evidence base. This is supported by the fact, for example, that the National Institute for Occupational Safety and Health (NIOSH), whilst citing many articles on beryllium on its website, does not offer any specific advice on health surveillance in beryllium workers, as it does for other industries.

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EXECUTIVE SUMMARY

Objectives

To review the current evidence for occupational health screening/surveillance in workers exposed to beryllium.

Main Findings

As exposure limits for beryllium have decreased, so has the incidence and severity of chronic beryllium disease.

There are however an emerging number of cases of subclinical disease and beryllium sensitization (BeS) that are being detected with new immunological tests, namely the beryllium lymphocyte proliferation test (BeLPT). Almost all the recent data on screening beryllium workers relates to the BeLPT, and more traditional screening programmes such as spirometry and chest x-rays that have been in use since the 1950s have only been evaluated as secondary endpoints.

Whilst the BeLPT has revolutionised the diagnosis of chronic beryllium disease (CBD), concerns have been raised about its inter- and intra-laboratory variability, possible reversibility in patients and uncertain sensitivity and specificity. There is also debate about the natural history of BeS and subclinical CBD and the ethical aspects of identifying disease early when there is no treatment, and subsequent employment implications. Another issue for the UK is the fact that only one laboratory offers BeLPT testing, although certain evidence supports double sampling of tests across laboratories to improve sensitivity and specificity. All these factors have led to certain US based groups advocating the use of BeLPT for screening and others not.

Therefore, in the US, a definitive stance on the content of a health surveillance programme has not been possible from the current evidence base. This is supported by the fact, for example, that the National Institute for Occupational Safety and Health (NIOSH), whilst citing many articles on beryllium on its website, does not offer any specific advice on health surveillance in beryllium workers, as it does for other industries.

Recommendations

The exact nature of any health surveillance programme should be based on local context and needs, and following a comprehensive risk assessment. The following general comments are justifiable from the evidence base.

If the intent of health surveillance is to identify early beryllium sensitisation as a marker of those at risk of progressing to CBD (or as a minimum to characterise sensitisation in a group of exposed workers), then by definition the programme must include the BeLPT with an appropriate occupational health policy to deal with positive results, including educating the workforce about the implications of a positive test. The natural history of Beryllium sensitisation is not fully understood, but in theory offers an opportunity to identify early immune responses, to decrease exposure and hence intervene to improve prognosis.

If the intent is to identify CBD alone (when fibrosis is established and the worker is potentially going on to develop progressive lung harm), then the evidence is mixed, but

probably supports a standard approach of symptom questionnaire, chest x-ray and lung function testing.

Any ongoing health surveillance programme should ideally be conducted in such a way as to contribute to the current evidence base, to better inform future health policy.

Uncertainties also surround the correct occupational health policy if abnormalities are found in surveillance testing. Logically one would suggest reduced exposure or redeployment away from exposed areas if either a positive BeLPT or other marker is identified but as yet there is no firm evidence that this approach is of long-term benefit.

Finally, the evidence base in this field is continually evolving as more is understood and published concerning the natural history of CBD, BeS, new immunological and genetic tests, and it is recommended that the evidence should be re-evaluated in 12 months time.

1 INTRODUCTION

Beryllium (Be) is an alkaline earth metal, that is silvery-grey in colour, strong yet lightweight, with excellent electrical and thermal conductivity. Due to these chemical properties it is often alloyed with other metals, and is widely used in a variety of industries (Table 1).

Table 1 Uses and application of Beryllium Ref. (1-3)

Technology	Application
Aerospace	Engines and rockets
	Brakes and landing gear
	Satellites and gyroscopes
	Precision tools
	Altimeters
	Mirrors
Energy and Electrical	Heat exchanger tubes
	Microelectronics
	Microwave devices
	Nuclear reactor components
	Oil field drilling devices
	Relays and Switches
Telecommunications	Undersea repeater housings
	Mobile phones
	Personal computers
	Transistor mountings
	Electrical connectors
	Switches and springs
	Electromagnetic shielding
Biomedical	X-ray tube windows
	Scanning electron microscopes
	Dental prostheses
	Medical lasers
Defence	Tank mirrors
	Springs on submarine hatches
	Mast mounted sights
	Missile guidance
	Nuclear triggers
Fire prevention	Non-sparking tools
	Sprinkler systems
Automotive	Air-bag triggers
	Anti-lock braking systems
	Steering wheel connectors
Miscellaneous	Plastic moulds
	Bellows
	Jewellery – aquamarine and emerald
	Golf clubs
	Bicycle frames
	Camera shutters
	Fishing rods
	Pen clips
	Scrap metal recovery and recycling
	Ceramics

In nature Be ore occurs in two forms, the silicate, bertrandite and the aluminosilicate, beryl. The majority of mined Be comes from the USA, China and Russia and it is not mined in the UK, so all current exposure in this country occurs during Be processing or manufacturing (3, 4).

Estimates of exposure to beryllium vary from country to country. An evaluation by Kauppinen (5) in the European Union suggested about 67,000 people were exposed through work in the early 1990's. An estimate in 2004 (6) suggested between 24,400 and 134,000 people currently working in government and private industry in the USA were potentially being exposed to beryllium at a level greater than 0.1µg/m^3 of beryllium in air. In the UK, estimates are lower with between 500 and 1000 people currently being exposed through work (7).

1.1 HEALTH EFFECTS

Beryllium has two main effects on the lungs; acute and chronic beryllium disease. Acute beryllium disease, presumed to be a chemical pneumonitis (or alveolitis) was first described in Europe in 1933 (8) and the USA in 1943 (9). This tends to present during or soon after exposure with dyspnoea, fever and radiological infiltrates. Usually acute beryllium disease resolves with removal of the exposure, although it can lead to a degree of chronic fibrosis (3, 10).

The second effect, chronic beryllium disease (CBD) was first described by Hardy and Tabershaw in 1946 (11), in fluorescent light bulb workers. It is a chronic granulomatous disorder affecting the lungs or skin, caused by a cell-mediated sensitization to beryllium. Clinically, CBD causes a dry cough, wheezing, dyspnoea, fatigue, and weight loss (2, 3). Additionally, there is a subclinical type of CBD, characterized microscopically by the presence of non-caseating granulomas and this is differentiated from clinical CBD by the absence of physical symptoms or chest X-ray or lung function changes (12).

Traditionally beryllium disease was classified by the Beryllium Disease Case Registry criteria, which addressed two areas:

1) establishment of significant beryllium exposure
    a. occupational history and/or results of air samples or
    b. the presence of beryllium in tissues or urine.
2) objective evidence of lower respiratory tract disease with at least two of the following
    a. clinical symptoms and course consistent with CBD
    b. characteristic histological changes in lung tissue or lymph nodes
    c. chest x-ray evidence of interstitial fibronodular disease
    d. decreased pulmonary function tests (obstruction or restriction and diminished diffusion capacity)

Therefore CBD was generally only diagnosed in those with clinical symptoms. Beginning with approximately 300 known cases in 1951, the Registry increased rapidly to include 606 cases by 1958, 760 cases by 1966, and 898 by 1983 (13, 14). Following exposure reduction in the 1950's, and the decrease in cases reported to the registry, it had been thought that CBD was becoming a disease of the past, however this myth was dispelled in the 1980's as further cases began to emerge at lower exposures and often picked up by new immunological testing techniques (2).

With the advent of these new tests (which will be described later), the term beryllium sensitization (BeS) was defined, in which individuals have a hypersensitivity reaction to beryllium, but no evidence of any respiratory disease (15). A proportion of people exposed to beryllium and its compounds can become sensitized, with the prevalence of beryllium sensitization in exposed worker populations ranging between 0.8% and 12% in various studies.

The prevalence of CBD in similar groups is lower than the sensitization prevalence, and has been reported to range between 0.4% and 8% (16). CBD has been shown to occur many years after first exposure (2, 17, 18), even if that exposure has ceased, and can occur even after fairly minimal exposure levels or so-called by-stander exposure (2). It can also occur quickly, within three months of exposure (19) and it is possible there may be a dose response relationship (20, 21) and a relationship to the type of workplace exposure (22). The percentage of those with BeS who have CBD at the time of initial assessment varies in different studies from 14% to 100% (17).

In recent years, as exposure to beryllium has been reduced, a new type of classification of beryllium health effects has been suggested:

<u>Diagnostic criteria for beryllium health effects</u>

1. Beryllium sensitization
    a. Evidence of a beryllium-specific immune response as indicated by
        - abnormal blood Be Lymphocye Proliferation Test (BeLPT) or
        - positive beryllium skin patch test
    b. No evidence of granuloma on lung biopsy

2. Subclinical CBD
    a. Evidence of a beryllium-specific immune response (see 1a above)
    b. Histopathological changes on lung biopsy consistent with CBD such as
        - noncaseating granulomas
        - mononuclear cell infiltrate
    c. No respiratory symptoms or physiological abnormalities

3. Clinically evident CBD
    a. 2a and b above for CBD *and*
    b. Clinical signs and symptoms, including
        - respiratory symptoms such as cough or shortness of breath
        - physical examination findings such as crackles on chest examination
        - chest x-ray abnormalities revealing a reticulonodular infiltrate
        - physiological impairment with abnormal pulmonary function testing, exercise testing, or gas exchange

Ref (15)

CBD was first postulated to be an immune-mediated disease in 1951 (23), and beryllium sensitization was initially defined by the beryllium skin patch test. However this test is not currently in widespread use in the surveillance of beryllium workers

because of concerns that the test itself might induce sensitization or worsen existing CBD (12, 15).

It is important to note when studying beryllium sensitization and airborne workplace exposures, that sensitization can occur through skin contact as well as inhaled particles and in the assessment and prevention of disease this needs to be taken into account (16). Also, there does seem to be a background rate of beryllium sensitization in some individuals that have not been occupationally exposed to beryllium. This may be expected because Be is widespread in nature, is present in some common materials such as tobacco or coal, and is used in some dental work. This has been confirmed in several studies, both in the US and Japan, (with skin patch testing as well the BeLPT) with estimates ranging from 1-5% (12).

To try and establish the natural history of BeS, a longitudinal study by Newman *et al* (17) monitored a cohort of beryllium-sensitized individuals at two yearly intervals, using bronchoalveolar lavage and repeated transbronchial lung biopsies to determine progression to chronic beryllium disease. In total, 55 people were followed up and 17 (31%) developed CBD within an average follow-up period of 3.8 years. Thirty-eight of the 55 (69%) remained sensitized but without disease after an average follow-up time of 4.8 years, and some people with BeS remained disease free up to 12 years later. In those who progressed, there was no difference in those who were still exposed to Be and those who were no longer exposed. No personal exposure monitoring data was available, but using work history information it appeared that workers with possibly higher or more consistent exposures (i.e. machinists) were more likely to progress to CBD. However two people, a secretary and a security guard had potentially only bystander exposure. Follow up in this study is ongoing.

A further study (24) followed a cohort of 136 beryllium oxide ceramic workers over an 11 year period up to 2003, including those who had since left employment. They were evaluated for beryllium sensitization and chronic beryllium disease. In 1992, the point prevalence was 6% sensitized and 4% CBD. Follow-up was maintained on 83% of the 128 not sensitized in the original testing. Corrected period prevalence for sensitization and CBD were 20% and 14%, suggesting a more than three fold increase in the observation period. However whilst useful, the numbers in these studies are relatively small.

Finally, there is also concern that beryllium exposure can cause lung cancer, and the Agency for Toxic Substances and Disease Registry (ATSDR) and the International Agency for Research on Cancer (IARC) have classified beryllium as a known human carcinogen, whilst the Environmental Protection Agency (EPA) classifies beryllium as a probable human carcinogen.

1.2 EXPOSURE LIMITS

Exposure limits were introduced in the USA in 1949 by the Atomic Energy Commission, with a daily weighted standard of 2 $\mu g/m^3$. The Occupational Safety and Health Administration (OSHA) later adopted this as a legally permissible limit but changed the time period to an eight hour average (14, 20, 25). Currently in the UK, the Control of Substances Hazardous to Health (COSHH) Regulations 2002 are set at this same level (26). Whilst it seems that these exposure limits have greatly reduced or even prevented the severe cases of CBD seen previously, they are clearly not protective against beryllium sensitization or subclinical CBD (14, 27).

This has led the American Conference of Government Industrial Hygienists to suggest new Threshold Limit Values of between 0.02 and 0.2 $\mu g/m^3$ (20, 28), the lower limit being based on a study by Kelleher (29, 30). In a study of exposure limits, Madl found that all workers with BeS and CBD had at least a 5% probability of experiencing beryllium exposures exceeding the 0.2 $\mu g/m^3$ level, and so concluded that maintaining exposures below 0.2 $\mu g/m^3$ 95% of the time may prevent BeS and CBD in the workplace (30). There is also evidence that better respiratory and skin protection in the workplace can reduce sensitization rates in the absence of any change in the airborne exposure levels (31).

2 METHODS

The aim of this review is to evaluate the current evidence for health surveillance in beryllium workers. Medline was therefore searched, from 1950 to the present day, using keywords and phrases (Appendix 2), in particular focusing on screening and surveillance, along with more specific terms relating to urine, chest X-ray, lymphocyte proliferation test and pulmonary function testing.

Also, as part of another ongoing literature review in which beryllium was already incorporated, various other databases (Appendix 3) were searched with the assistance of the HSE information centre. Two hundred and twenty two articles came up in the search, and the titles and abstracts were reviewed for relevance. All those felt to be of use were entered into Endnote software to aid tracking of references. The relevant articles were then reviewed, concentrating initially on the most recent and review articles. Where it was felt appropriate, references and citations from articles were also sought. In total 123 articles were considered to have some relevance, and entered into Endnote.

3 RESULTS

For a condition that has become increasingly rare over the last 50 years, there is a considerable amount of published data on the health effects of beryllium and surveillance or screening amongst workers. The vast majority of this in recent years is from the USA and relates to the beryllium lymphocyte proliferation test. Each potential area for screening will be dealt with separately.

3.1 BERYLLIUM LYMPHOCYTE PROLIFERATION TEST (BELPT)

In the 1970's *in vitro* immunological testing that resembled the skin patch test began to be developed (32, 33), but it was 1989 when the beryllium lymphocyte proliferation test was first really suggested as a screening blood test to identify subclinical beryllium disease (34). Prior to this, the test had been discounted as a potential screening tool because the positive cases had normal radiology or lung function testing or due to poor reproducibility of the test. However, with more advanced techniques, in particular the advent of the transbronchial biopsy, positive tests could now be compared to a tissue diagnosis of subclinical beryllium disease (34).

Initially the test was known as the beryllium-specific lymphocyte transformation test, as it was felt that the lymphocyte growth seen may be a malignant process rather than normal growth (10). The test can be performed on peripheral blood and also on cells from bronchial alveolar lavage. To perform the BeLPT, T-lymphocytes are incubated in three concentrations of beryllium sulphate over two different time periods. If beryllium is present, then sensitized lymphocytes are stimulated to take up thymidine labelled with tritium, which increases the radioactivity of the samples. Six ratios (stimulation index) are generated by comparing the radioactivity of the samples incubated with beryllium sulphate with those incubated without. If none of the six ratios are raised, then the test is considered to be normal. One elevated ratio is considered to be a borderline abnormal result and if two or more ratios are elevated this is considered to be an abnormal test result. If the blood sample is not adequate for testing, the test is indeterminate and needs to be repeated with a fresh blood sample (35, 36).

The paper by Kreiss *et al* (34) evaluated the test in 51 workers with current Be exposure from a work force of 5000 at a company where three cases of chronic beryllium disease had been identified in former workers. Six were found to have abnormal BeLPT, and compared to the non-sensitized workers they had a longer exposure time to Be (average 23 years vs. 11 years). Five of them consented to invasive investigation and four of them were found to have CBD as defined by granuloma on transbronchial biopsy. None had been picked up in a yearly surveillance programme that included chest x-ray, examination and basic spirometry. The authors concluded that the BeLPT appeared to be more sensitive than the other screening tests used previously, however the natural history of subclinical beryllium disease would need defining before the test could be recommended for a workplace screening tool. Since this paper the BeLPT has been introduced in certain industries in the USA, of which some examples will be given below.

Markham *et al* (37) screened 641 workers at a beryllium production facility in 1994 – 1995 and found 52 of the 637 who completed the testing had abnormal BeLPT. Of these, 48 progressed to full clinical evaluation and 20 had evidence of CBD, whereas four had abnormal BeLPT but no evidence of granuloma on biopsy on repeated occasions. This paper also evaluated two different laboratories and found that lab A

recognized 71% of the cases, lab B 46% and both together only 21%, concluding that the use of a single laboratory for the screening test was questionable and that two laboratories testing split samples greatly improved the sensitivity. This was later confirmed by Middleton *et al* (38) who demonstrated that splitting the initial sample between two laboratories could enhance the sensitivity of the testing.

Newman *et al* (19) report on a surveillance programme at a beryllium machining plant that was commenced in 1995. New employees were tested within the first three months of employment, and others every two years. Those who had two abnormal tests were referred for clinical evaluation and further investigation. In total 235 employees were screened from 1995 to 1997, of whom 15 (6.4%) had confirmed abnormal BeLPT results indicating beryllium sensitization. Eight of these employees had biopsy proven chronic beryllium disease. Four of the 15 cases were diagnosed within three months of first exposure to beryllium. Of those originally tested 187 participated in further two yearly screening in 1997 and 1999. Seven more developed beryllium sensitization or chronic beryllium disease, increasing the overall rate to 9.4% (22 of 235).

All of the cases with abnormal BeLPTs had normal spirometry. None of the cases required treatment, possibly because they were picked up in the early stages of the disease, and their exposures then modified. The authors concluded “The blood BeLPT should be used serially in beryllium disease surveillance to capture new or missed cases of sensitization and disease. Beryllium sensitization and chronic beryllium disease can occur within 50 days of first exposure in modern industry”.

In 1991 voluntary BeLPT testing started at the Department of Energy’s Rocky Flats nuclear weapons complex amongst current and former workers (39). Between June 1991 and October 1994, 1805 current employees had their initial BeLPT as participants in the screening programme. Seven cases of CBD were diagnosed, and 28 were identified as being beryllium sensitized. During the same period, 2463 former employees received a BeLPT. In this group, 20 individuals were diagnosed with CBD and 46 former employees were identified as being sensitized to beryllium. The total sensitization rate (CBD and sensitized cases) for the tested cohort (n=4268) was 2.3%.

The CBD rate was 0.6% and the beryllium sensitization rate was 1.7%. These rates are comparable to rates reported in other studies of beryllium-exposed workers (39). For the 27 individuals diagnosed with CBD, only one had a chest x-ray compatible with CBD, and for the 74 beryllium-sensitized cases, three were compatible. Further data from the Rocky Flats surveillance scheme was presented again in 2001 (40) in greater detail. In total 18,589 living current and former Rocky Flats employees were contacted, of which 6614 eventually participated and received at least one BeLPT. The total beryllium sensitization rate for the 5173 people that received an initial BeLPT and/or three year BeLPT was 4.5 % compared to the 2.3% reported in the first study.

Stange *et al* (36) analyzed 25,643 BeLPT results in 12,184 participants from 1992 to 2001 for current and former employees at 18 Department of Energy sites to evaluate the efficacy of the BeLPT for determining beryllium sensitivity and CBD. These sites represented a variety of beryllium exposures, and included beryllium, beryllium oxide and beryllium-copper alloy. Four hundred and fifty eight people with no known beryllium exposure were also included in the analysis. 4.1% of the results were unsatisfactory or uninterpretable. This study found that the overall inter-laboratory agreement of the four BeLPT laboratories for all results ranged from 93.8% to 98.1%, and the range of agreement for abnormal results ranged from 26.2% to 61.8% (kappa 0.42 to 0.61). False negatives ranged from 25% to 38%, and false positives were calculated to be

1.09%, with a laboratory range of 0.00% to 3.35% over the 10-year period. BeLPTs performed on inter-laboratory split blood specimens from sensitized individuals showed a false negative rate of 31.7%. The intra-laboratory repeatability of abnormal BeLPT results ranged from 80.4 to 91.9%. The sensitivity of the BeLPT was determined to be 0.683, with a specificity of 0.969. The authors and other commentators have however suggested it is difficult to accurately define the sensitivity and specificity for this test, because the BeLPT is the only practical means to determine beryllium sensitivity and as such, there is no other gold standard test with which to compare it to (33, 36, 41).

In a review article, Borak has made an attempt to comment on this, citing the inconsistency in results in retesting in both the Welch and Stange papers (36, 42), with retesting only confirming between 11.5% and 100% of results depending on the stimulation index used. Middleton *et al* (38) used statistical analysis on the Rocky Flats data to evaluate two different testing algorithms, the first involving a single test on the initial sample, and the second involving splitting the initial sample. They came out with values of 66% sensitivity for the basic algorithm, and 86% for the second algorithm. False positive rates were quoted at less than 1 in 1,000. For CBD, comparisons are also difficult, with different studies using different criteria for making the diagnosis of CBD, and estimates can be found for the positive predictive value that vary from 11% to 100% in various studies (18, 42-45).

The BeLPT has been in use now since 1987 and began to be used in screening or surveillance programmes in the 1990's (19, 39). A review article by Kreiss in 2007 indicated that it has been used in over 15 separate studies, looking at screening for sensitization, the epidemiology of workplace exposures, and the effectiveness of workplace interventions to reduce sensitization (2). Despite this, although used in some areas, its use is not universal. For example the US Department of Energy has initiated a comprehensive surveillance program to identify and prevent beryllium disease at its facilities (36), and Brush Wellman, one of the largest beryllium miners, manufacturers and processors instituted the BeLPT in 1992 (12). On the other hand, the US Department of Defense policy statements have discouraged the use of the BeLPT for surveillance of exposed workers (38).

There have been concerns about use of the BeLPT for some time, summed up well in three recent review articles. The first from Borak *et al* (43) in 2006, focused on the question "is the BeLPT a good test for screening asymptomatic individuals". To do this, they used five criteria adopted by the World Health Organization (46) and refined by the US Preventative Services Taskforce (47) namely:

i. Does the disease cause a burden of suffering?
ii. Is the screening test accurate and reliable?
iii. Is there a benefit to early disease detection?
iv. Is the screening harmful?
v. Do the benefits out weigh the harms?

i. <u>Does the disease cause a burden of suffering?</u>

This is difficult to weigh up in the modern age, as a lot of the data on CBD mortality is old. Clearly in the 1950s it was a very serious diagnosis, with reports of about a third of those with the disease dying from it (48). However exposure limits have been reduced dramatically since then and better preventative measures are in place. Indeed Maier in 2001 quotes "Past mortality rates varied from 5% – 38%, (however) currently most individuals with CBD die from other causes" (15). Prevalence rates of both CBD and

beryllium sensitization are also difficult to ascertain accurately, as many workers have been reported in more than one study (43).

ii. Is the screening test accurate and reliable?

In the UK, only the Royal Brompton Hospital in London currently offers the BeLPT, and in the USA, only four facilities perform the test (35). Concerns have been raised by several authors as well as Borak about poor inter and intra-laboratory variability, with the use of similar but not identical protocols and a varying positive predictive value and sensitivity and specificity of the test (2, 36, 43, 44, 49). Donovan (12) concurs with Borak's assessment, stating in the introduction to his study "unfortunately, the BeLPT has a number of shortcomings that limit its usefulness and complicate the interpretation of worker surveillance programs and studies. It is widely recognized that the BeLPT can yield false negative results, and the test is known to be subject to substantial intra- and inter-laboratory variability (15, 22, 36, 44, 49, 50). In 2001, a consensus led by the Beryllium Industries Scientific Advisory Committee recommended to the United States Department of Energy a standard on BeLPT materials and procedures, but despite this recommendation, there continues to be no uniform procedure that laboratories use to perform the test. There is also no quality control to ensure the various laboratories generate consistent findings for the same sample" (12).

Donovan also found evidence in his study, of reversibility in the test. More than 10,000 BeLPT results from nearly 2,400 participants were analyzed. The samples came from four different beryllium mining, manufacturing, or processing facilities, (but all part of the same company – Brush Wellman) as part of its medical surveillance program. They found the prevalence of confirmed BeLPT positive results was highest in the first year of employment, and a peak in the prevalence of positive results was seen during the first four to eight months of employment. Normal BeLPT results were observed in many workers that had previously tested positive, suggesting the test is reversible. This has also been shown in five other studies, although they were then thought to be false positives or negatives (12). The conclusion of Donovan's article states "although, the BeLPT can be used to help characterize beryllium sensitization in worker populations, it does not appear to be a reliable indicator of sensitization in individual workers, especially when it is administered in the context of a screening study. The American Conference of Governmental Industrial Hygienists Biological Exposures Indices Committee has assessed the BeBLPT and did not recommend its use as a biological indicator to assess exposure and health risk to workers".

iii. Is there a benefit to early disease detection?

Again evidence here is limited and whilst steroids are sometimes used for treatment, they have not been subjected to a randomised control trial (43). There is also no evidence that treatment changes the natural history of subclinical CBD or BeS. Whilst removal from further exposure has been recommended (and appears sensible), there is again no evidence as to whether this improves outcome (43), especially as progression to CBD can occur years after exposure has ceased.

iv. Is the screening harmful?

Whilst the actual blood test is not harmful in itself, it is inconvenient and may need repeating due to poor reliability, up to 3.6% of tests in one study (18), and 4.1% in Stange's study (36). There is also the issue of false positives, with the anxiety and potential workplace effects e.g. being moved unnecessarily to a different job (51). A

further consideration is the potential cumulative false positive risk if tests are repeated every two to three years in a screening problem. Then, even if the test is confirmed, there is no guarantee that a positive BeLPT and Be exposure means respiratory abnormality, with one study showing only 25% of cases with Be exposure and a positive BeLPT had CBD at bronchoscopy (49). Finally, the duration of follow up needs to be taken into account. As CBD can occur many years after exposure has ceased, once people start in a screening programme, it could be argued that follow up should be lifelong.

v. Do the benefits outweigh the harms?

This remains subjective, but in his review of the evidence Borak concluded, "it is therefore inappropriate (and perhaps unethical) to recommend its use for routine screening". This was due to the lack of evidence of benefit, although he did conclude that there might be a role for surveillance as opposed to screening, although again the clinical benefit on current evidence remains undetermined.

Some authors do however feel that there is enough information to recommend screening. In their discussion Welch *et al* say "screening workers with potential beryllium exposure using a blood BeLPT test is generally accepted as a valid indicator of both exposure and probability of developing subsequent CBD. CBD of the lung can be disabling, even fatal and treatment at an early stage for similar granulomatous diseases of the lung, such as sarcoidosis, can prevent disease progression. There is, therefore, a clear rationale for early detection of CBD, and a clear reason to screen for sensitization in populations at risk for CBD" (42).

Cullen in an editorial in 2005 entitled "Screening for Chronic Beryllium Disease: One Hurdle Down, Two to Go" makes the point that there remains no evidence that intervention after a positive test e.g. removal from exposure makes any difference to long term outcome, and the natural history for CBD and BeS in the present day remains undetermined.

He concludes, "Pending the outcome of these further observations, many may continue to advocate using the test for the very reasons it was originally adopted. It would be difficult to fault such a posture so long as renewed efforts are made to ensure that those administering and interpreting the test, as well as those being tested, understand that neither the clinical implication of a positive test nor the benefit of any action advised as a result is based on strong scientific evidence, other than the need for a full baseline pulmonary evaluation and regular follow-up care" (52). However in replies to this editorial, both Takaro and Newman point out that some of those workers with CBD have shown decreases in respiratory physiology over time, therefore there is a clear case for screening and early intervention (53).

Kreiss, who has performed much of the work in this field since the original 1989 paper, co-authored a review article in 2007. The authors conceded, "debate about the BeLPT for worker screening continues", however they felt that current beryllium exposed workers may benefit from screening as they can then choose to limit further exposure if sensitized. There is no evidence however, that this will improve long-term outcome as by the time of sensitization they may well have already accumulated enough lung Be to develop CBD. As treatment of CBD with corticosteroids is generally reserved for advanced disease, there is no clinical benefit from an earlier diagnosis, and there are potential social and psychological harms from giving a person an early diagnosis before treatment is indicated. The authors go on to say "in current beryllium workers,

screening for sensitization is prudent, although no evidence exists thus far that identification of sensitization or subclinical beryllium disease changes prognosis, either by removal from exposure or by treatment, which is usually given only when objective impairment can be demonstrated and tracked. However, screening can be the basis of surveillance, in which risk of sensitization by subgroup within the workforce can be used to identify higher risk areas for prevention measures" (2).

What is clear, is that current opinion over whether or not the BeLPT should be used for screening is divided. Whilst no-one seems to disagree that the test is currently the best available and is very useful at detecting subclinical CBD, there are too many other variables in play to recommend the test categorically, and this is only likely to change with time as we learn more about the natural history of the disease and testing methods are improved.

3.2 GENETIC SUSCEPTIBILITY

There is now good evidence that susceptibility to chronic beryllium disease has a genetic component. Human Leukocyte Antigen (HLA) with a single amino acid variation at position 69 on the HLA-DPß1 gene confers a higher risk of chronic beryllium disease and sensitization (54, 55). Approximately 80% of patients with CBD have this genotype compared to about 40% of the general population. However, at present, due to the relatively high prevalence of this genotype in the population combined with the relatively low prevalence of chronic beryllium disease it cannot be used as a reliable screening tool (2, 54, 56). There are also ethical considerations to take into account, concerning protection of worker confidentiality, and potential employment issues, so genetic testing of beryllium workers is felt to be inappropriate at present (57-60).

3.3 BERYLLIUM ANTIBODY ASSAY

In the early to mid 1990's a test was developed to identify antibodies in the blood to beryllium, and this was put forward as a screening test, and used in two case studies (61). It seems however to have fallen from favour with no recent publications in this area.

3.4 RADIOLOGY

Chest x-rays have been used historically for medical surveillance in beryllium exposed workers and are recommended in some older (3) and more recent text books (62). The x-rays are read using the International Labour Organization scale for pneumoconioses and defined as abnormal if there is a profusion of opacities of 1/0 or greater on this scale (34, 63). The majority of papers published in the last 20 years with regard to screening or surveillance are on the BeLPT, and one has to try and extract information on radiology from these papers. Also, most of the recent work that focuses on the BeLPT is looking at BeS or subclinical CBD, which by definition (as outlined in the introduction) will have normal radiology. Another concern with using radiological surveillance, especially when compared to newer techniques such as BeLPT, is the degree of sensitivity and specificity. In a case series, 46% of those with biopsy-proven CBD had normal chest x-rays, and even high resolution CT scanning of the lungs is normal in up to 25% of patients with CBD (64). A recent case report (65) showed chronic beryllium disease in a patient with a normal chest x-ray.

An observational study of 1,786 workers at the Nevada test site that involved work history questionnaires and BeLPT found a prevalence of BeS of 1.3% among former

workers who participated in this screening program. There was no difference in pulmonary function, chest X-ray abnormalities, or respiratory symptoms between those who were sensitized and normal (20).

In Kreiss's original study (34), of the six people with positive BeLPT, only two had an abnormal chest x-ray, although this was retrospective, and had not been picked up on routine medical surveillance.

The Cardiff Atomic Weapons Establishment used surveillance as an integral part of their beryllium control program from the facility's inception in 1961. The surveillance program included monthly spirometry, an annual physical examination, and annual x-rays until the mid 1980s, after which time they were only provided when requested (66). It is unclear from the paper why the chest x-rays were stopped, but it seems reasonable to conclude that the occupational health physicians felt they were no longer necessary, although this may be because only one case of CBD was ever diagnosed there, which followed a Be contaminated skin laceration.

Newman *et al* quote "the point-prevalence of abnormal BeLPT results in the beryllium using industry ranges from 1.8% to 11.8%, and for CBD from 1.8% to 7.8%. The test has proved to be more sensitive and specific than historic screening methods such as chest radiography, physical examination, and spirometry" (19).

Whilst on current evidence, few seem to suggest chest x-rays alone, some authors however do advocate the use of chest x-rays alongside the BeLPT. In a company that had manufactured beryllia ceramics from 1958 until 1975, nine new cases of CBD were found among 505 current and former employees. Two of these cases had either a normal or inconsistently abnormal BeLPT and were identified for diagnostic workup by their abnormal chest x-ray. The authors conclude "our data support efforts to prevent beryllium disease by lowering beryllium exposures and to identify subclinical and early disease by broad-based medical surveillance using the blood beryllium lymphocyte test and chest radiograph in beryllium-using industries"(18). A further study also identified two cases of CBD picked up on x-ray rather than BeLPT and came to a similar conclusion (40).

As part of the Rocky Flats surveillance, 4255 chest X-rays were evaluated according to the ILO classification system. Of the X-rays for the 27 people found to have CBD, only one had a small opacity profusion of 1/0 or greater, one was rated 0/1, and the remaining 25 were rated as 0/0. Of the 74 with BeS, X-ray results found three people with small opacity profusion of 1/0, one with 0/1, and the final 69 were rated as 0/0. Only one case of CBD was identified in which the chest X-ray findings indicated CBD that had not already been suggested by the blood BeLPT.

Again the authors concluded "The chest X-ray was nonspecific for the diagnosis of CBD in this population of workers. These observations are similar to those reported elsewhere. Based on these data, the posterior/anterior chest X-ray should not be the sole means of screening for CBD or beryllium sensitization in an occupational beryllium health surveillance program" "Since chest X-rays have not been useful in identifying early disease, they need not be routinely done" (39, 67)

In summary, it is difficult to make historical comparisons, as the majority of patients identified at present are picked up early due to the BeLPT. With the occasional exception, the chest x-ray does not seem to contribute significantly to the screening

process and current evidence would seem to be it has a use as an adjunct to BeLPT, but not instead of or on its own.

3.5 RESPIRATORY FUNCTION TESTING/SPIROMETRY

The same issues apply to spirometry as to radiology in that it been a secondary study point in the recent literature. Referring again to Kreiss's original paper (34), of the four patients found to have histologically proven CBD, all of them had normal basic spirometry. The paper states, "the physiological abnormalities among these four case subjects were subtle and in one case nonexistent". Although on direct questioning they admitted to exertional breathlessness, none of them had sought medical attention with regard to this, and none had been picked up in a screening programme that included yearly examination, chest x-ray and basic spirometry. Likewise in Newman's 2001 study (19) none of those with disease had abnormal spirometry.

One detailed study, compared surveillance identified early beryllium disease patients detected using the blood BeLT, with clinically identified beryllium disease patients who presented with symptoms or x-ray abnormalities. They measured spirometry, lung volumes, diffusion capacity, arterial blood gases, and maximal exercise capacity. Physiological abnormalities occurred in 12 out of 21 (57%) of the surveillance identified patients, however these were generally subtle or found on exercise testing and none of the patients had a pure restrictive defect, and only one of 21 had an abnormal diffusing capacity (68).

Referring to the Nevada test site workers again, of the 1,786 former workers tested for BeS, 23 had a confirmed positive result. There was no difference in pulmonary function, chest X-ray abnormalities, or respiratory symptoms between those who were sensitized and normal (20).

Physicians from the Medical Research Council pneumoconiosis unit tried to address the usefulness of pulmonary function testing with longitudinal follow up over 30 years at a beryllium ceramics factory in South Wales (69). The workers had chest x-rays, history and examination and detailed respiratory physiology, including full lung function testing with transfer factor, static lung compliance testing using an oesophageal catheter and submaximal exercise testing. The numbers studied were not sufficient to come to definitive conclusions, however, of the six cases of CBD found, all six had chest x-ray changes, compared to lung function abnormalities in only four, leading the authors to conclude "these and other related observations suggest that while the lung function may contribute to diagnosis and management of suspected clinical cases it is much less useful than radiography for routine surveillance".

A cross-sectional study of 297 beryllium workers in the 1980's (70) found a correlation between beryllium exposure and decrease in FEV_1 and FVC, and although these findings have been replicated in another study (71), three others have not found this link (69, 72, 73). They also assessed the alveolar arterial oxygen gradient from arterial blood gases and found an initial increase, suggesting changes at the alveolar–capillary level, although with workers who had been there longer than 10 years, the levels returned to normal. A variety of reasons were postulated for this, including the possibility of a reversible effect from beryllium in the initial stages of exposure, along with the suggestion that these results may be due to selection bias or the healthy worker effect.

Twenty two workers were studied with a variety of tests by Aronchick *et al* (74) to try and correlate radiology with lung function testing. Only the 17 who had a positive BePLT were included in the final analysis, and of these 14 had histological evidence of CBD. No correlation was found between chest x-ray abnormalities and duration of exposure, vital capacity or transfer factor. The only positive correlation was the unsurprising finding that extensive pleural disease was linked to a reduced vital capacity.

To summarise, again the evidence for spirometric screening is poor, although one could argue there is at least no harm from this test e.g. unnecessary radiation.

3.6 URINE

There is relatively little data published in recent years on the use of urinary Be levels to screen for the risk of developing chronic beryllium disease.

A study in 2000 (75) investigated the use of urinary Be measurements in 65 workers in two electric steel plants and two copper alloy foundries, who were exposed to fairly low levels of beryllium, as well as reviewing some of the previous literature. They found a correlation between exposure to Be and the level in the urine, but concluded that there was currently insufficient data to propose a Biological Exposure Index for urinary Be. This was due mainly to the fact that previous “normal” values for urinary Be in the literature were felt to be inaccurate due to the poor sensitivity and specificity of previous analytical methods and the small numbers in studies. The authors concluded that urinary Be may have a role in conjunction with other tests and on an individual basis to aid health surveillance programmes or aid diagnosis.

Wegner et al (76) investigated 57 German gemstone workers in 12 different factories. Despite previous thoughts that the beryllium released from grinding beryl gemstones (emeralds and aquamarines) was in an insoluble silica complex, increased levels of Be had been reported in the air. The authors measured a variety of parameters, including urine with direct electro-thermal atomic absorption spectrometry, lung function, chest x-rays, and the BeLPT. For the urine, this new spectrometry test had a detection threshold of 0.06 µg/l of Be in urine. The workers were split into two groups according to exposure, more or less than four hours per week. Urinary Be was not detectable in those with less than four hours per week exposure, and detectable in 17 out 27 of those with more than four hours per week exposure. Of these positives, one had a positive BeLPT, but there were no spirometrical or radiological abnormalities. The authors did find however, the stimulation indices in the BeLPT were slightly but significantly higher in cutters with detectable beryllium concentrations in the urine (>0.06 µg/l) than in subjects with concentrations below the detectable concentration.

They concluded that, grinding and cutting of gemstones containing beryllium may lead to airborne beryllium concentrations above current threshold limit values, and incorporation of beryllium could be shown in most subjects working more than four hours per week with beryls. Considering a positive BeLT in one subject and significantly higher beryllium stimulation indices in cutters with detectable beryllium concentrations in urine, they suggested improvements in workplace ventilation accompanied by routinely performed beryllium measurements in urine.

Both of these papers are from 2000, and none of the recent review articles on Be screening mention the role of urinary testing. There have however been recent improvements in this field, and several centres (including HSL) can now accurately

detect urinary beryllium. What is not known yet however is how the detection of small quantities of Be in the urine relates to the risk of developing BeS or CBD, although it does imply a degree of beryllium exposure. Due to the concern about the reliability of urinary testing in older papers, and lack of much recent data, there seems no justification for this test in health surveillance of beryllium exposed workers at present.

3.7 SARCOIDOSIS

Whilst clearly not a screening test, it is worth making a brief note about sarcoidosis. This disease and berylliosis have many clinical and pathological similarities and can be difficult to distinguish (77-81). It is reliant on a careful clinical history to confirm exposure, exclusion of other causes and confirmation of beryllium sensitization by BeLPT, or alternatively showing beryllium in lung tissue from open biopsy or autopsy. There are several reports in the literature of berylliosis initially being labelled as sarcoidosis (82), and a study in Israel in 2003 suggested 6% of patients given the diagnosis of sarcoidosis actually had CBD. It is worth bearing this in mind, as it potentially will increase the prevalence pool of those who actually have CBD and should be looked for in any investigation into the health of beryllium workers.

3.8 FUTURE DEVELOPMENTS

Attempts have been made recently to revise and improve the diagnostic criteria for the BeLPT, including the use of statistical control methods (41), and in 2006, the Agency for Toxic Substances and Disease Registry convened a panel of experts to consider the diagnostic criteria for the BeLPT (35). Developments are ongoing with new techniques and new reagents for this test such as flow cytometry (50, 83-85), and further advances in genetic testing may also play a role in the future. Longitudinal studies of the BeLPT are ongoing and we will learn more about the natural history of this disease with the passage of time.

4 CONCLUSION AND RECOMMENDATIONS

Beryllium has been recognised as being hazardous to health for 75 years now, and whilst exposure control limits have eradicated the acute toxic effects, there remains a chronic form of beryllium disease. This occurs in individuals who develop a systemic hypersensitivity to beryllium, and there is evidence of a genetic component in this. Screening and surveillance systems have been in place for many years and have included chest x-rays, spirometry testing, symptom questionnaires, physical examination, and more recently immunological testing. A lot of these were introduced in the 1950's when people really began to appreciate the potential harm of beryllium, and before the advent of evidence based medicine.

There is now a large body of evidence in health surveillance/screening in workers exposed to beryllium, most of which over the last 20 years relates to the BeLPT.

A current definitive stance regarding health surveillance is not possible, supported for example by the National Institute for Occupational Safety and Health (NIOSH) website, which whilst citing many articles on beryllium does not offer any specific advice on health surveillance as it does in other situations.

The exact nature of any health surveillance programme should be based on local context and needs, and following a comprehensive risk assessment. The following general comments are justifiable from the evidence base.

If the intent of health surveillance is to identify early beryllium sensitisation as a marker of those at risk of progressing to CBD (or as a minimum to characterise sensitisation in a group of exposed workers), then by definition the programme must include the BeLPT with an appropriate occupational health policy to deal with positive results, including educating the workforce about the implications of a positive test. The natural history of beryllium sensitisation is not fully understood, but in theory offers an early opportunity to identify early immune responses, to decrease exposure and hence intervene to improve prognosis.

If the intent is to identify CBD alone (when fibrosis is established and the worker is potentially going on to develop progressive lung harm), then the evidence is mixed, but probably supports a standard approach of symptom questionnaire, chest x-ray and lung function testing.

Any ongoing health surveillance programme should ideally be conducted in such a way as to contribute to the current evidence base, to better inform future health policy.

Uncertainties also surround the correct occupational health policy if abnormalities are found in surveillance testing. Logically one would suggest reduced exposure or redeployment away from exposed areas if either a positive BeLPT or other marker is identified but as yet there is no firm evidence that this approach is of long-term benefit.

Finally, the evidence base in this field is continually evolving as more is understood and published concerning the natural history of CBD, BeS, new immunological and genetic tests, and it is recommended that the evidence should be re-evaluated in 12 months time.

Summary of the current available tests

Test	Advantages	Disadvantages
BeLPT	1) Currently the most sensitive screening test available 2) Samples easy to obtain 3) Potential to pick up sub-clinical disease and allow exposures to be modified	1) Not widely available – currently only performed in one centre in the UK 2) Concerns have been raised about the variability of the test, and it is recommended to be performed with split samples going to two separate centres 3) The natural history of BeS remains uncertain so the benefits of early detection remain debatable. 4) Potentially exposes workers to unnecessary invasive investigations if false positive result obtained
Genetic testing	1) Potentially allows those at greatest risk of developing CBD to have exposures modified	1) Currently the relevant genotype is too widespread in the population 2) Ethical difficulties in performing the test
Urine levels	1) Easy to perform	1) Currently very little evidence of any benefit in screening 2) Accurate testing not widespread
Chest x-rays	1) If abnormal, is detecting a clinically relevant disease early 2) Cost effective to perform	1) Poor sensitivity 2) Cumulative radiation dose in young people
Spirometry	1) Cheap and easy to perform on site	1) Only reliable if performed well and due to potential +/- 3% variability in testing need data often over a few years 2) Poor sensitivity and specificity for health endpoints
Full lung function testing/exercise testing	1) Potential to pick up abnormalities earlier than simple spirometry	1) Difficult to do on site, so potential expense

5 APPENDICES

1) Summary of studies on BeLPT to 2007. {From Kreiss et al (2)}

Table 1 Percent prevalence of beryllium sensitization and disease by industry and study

Study and industry	N[a]	BeS (%)[b]	CBD (%)[c,d]	Comments
Cross-sectional studies of current workers				
Kreiss et al. 1989 (31) Nuclear weapons facility	51	6 (11.8)	4 (7.8)	[a]study limited to production and research and development machinists only; same facility as (29, 60, 62) [b]BeS classification based on single abnormal lymphocyte transformation test [d]83% of BeS (5/6) were evaluated with bronchoscopy
Kreiss et al. 1993 (29) Nuclear weapons facility	890	18 (2.0)	15 (1.7)	[a]same facility as (31, 60, 62); stratified random sample not previously tested [b]BeS included 1 with inconsistently abnormal tests; confirmed abnormal = 1.9% (17/890) [c]CBD included 1 BeS who refused bronchoscopy but who had skin wound and ventilatory abnormalities [d]94% of BeS (16/17) evaluated with bronchoscopy; study also evaluated 22 with radiographic abnormalities, 1 of whom had CBD
Kreiss et al. 1996 (28) Berylia ceramics	136	8 (5.9)	6 (4.4)	[a]same facility as (22) [b]1 BeS had initial normal BeLPT, found to be BeS 16 months later [c]CBD included 1 who was diagnosed later (see above), on second bronchoscopy [d]100% of BeS evaluated with bronchoscopy
Kreiss et al. 1997 (30) Be metal, alloy and oxide production	627	59/627 (9.4)	29/632 (4.6)	[b]BeS classification based on single abnormal BeLPT; confirmed abnormal = 6.9% (43/627) [c]CBD included 5 diagnosed prior to survey; 3 identified during survey had abnormal BALLPT only (no granulomas); granulomatous CBD identified during survey = 3.3% (21/627) [d]80% of BeS evaluated with bronchoscopy
Henneberger et al. 2001 (22) Berylia ceramics	151	15 (9.9)	8 (5.3)	[a]same facility as (28); 77/151 were in both surveys, none of whom had BeS or CBD previously [c]CBD included 3 with abnormal BALLPT only (no granulomas); granulomatous CBD = 3.3% (5/151) [d]93% of BeS (14/15) evaluated with bronchoscopy
Deubner et al. 2001b (10) Mining/extraction	75	3 (4.0)	1 (1.3)	[b]BeS included 1 with abnormal BALLPT only, identified during previous bronchoscopy; confirmed abnormal = 2.7% (2/75) [d]clinical evaluation offered to 5 workers: 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 diagnosed with CBD, 1—no CBD)
Sackett et al. 2004 (52) Nuclear weapons facility	2221	19 (0.9)	2 (0.09)	[a]same facility as (29), (31), (60) and (62), but workers were decontamination and decommissioning workers [d]42% of BeS (8/19) evaluated with bronchoscopy
Schuler et al. 2005 (55) Copper-beryllium alloy finishing	153	10 (6.5)	6 (3.9)	[b]BeS included 1 with CBD diagnosed just prior to survey, 1 diagnosed after survey; excluded 9 with likely false positive BeLPTs; survey BeS including latter = 11.2% (17/152) [c]CBD included 2 workers diagnosed pre- and postsurvey (see above) [d]94% with confirmed abnormal BeLPTs (16/17), plus pre- and postsurvey cases of CBD, evaluated with bronchoscopy
Stanton et al. 2006 (63) Copper-beryllium alloy distribution	88	1 (1.1)	1 (1.1)	[a]included workers from 3 distribution centers [d]100% of BeS evaluated with bronchoscopy

Cross-sectional studies of current and former workers				
Kreiss et al. 1993b (32) Beryllia ceramics	505	9 (1.8)	9 (1.8)	[a]included both current and former workers [b]BeS included 1 with single abnormal BeLPT; confirmed abnormal = 1.6% (8/505) [d]100% of BeS (8/8) evaluated with bronchoscopy; study also evaluated 10 with abnormal radiographs, 1 of whom had CBD
Welch et al. 2004 (73) Nuclear weapons facilities	3842	54 (1.4)	5 (0.1)	[a]included current and former workers from 3 sites; workers were construction trade workers [c]CBD included: 2 with abnormal BALLPTs and lymphocytosis; 1 with abnormal BALLPT and skin granulomas; 1 with normal BALLPT, pathologic abnormalities on biopsy and abnormal lung function; and 1 information was not presented [d]Authors did not state how many BeS were evaluated with bronchoscopy; authors stated 15% of the evaluated had CBD (5/33 = 15%), so we estimated 33/54 (61%) were evaluated
Rosenman et al. 2005 (50) Beryllium extraction, metal and oxide production	577	84 (14.6)	44 (7.6)	[a]included former workers only, who worked between 1957 and 1978 [b]all BeLPTs, including confirmatory tests, conducted at a single laboratory [c]CBD included 12 with "probable" CBD (no granulomas but abnormal BALLPT and/or upper lobe fibrosis); 9 diagnosed prior to study [d]all with confirmed abnormal BeLPTs and/or abnormal radiographs (n = 110) referred for bronchoscopy, 51% (n = 56) consented; evaluation for 9 diagnosed presurvey not presented
Longitudinal studies				
Stange et al. 1996 (60) Nuclear weapons facility	4397	107 (2.4)	29 (0.7)	[a]same facility as (29), (31) and (62); included current and former workers; study involved initial testing plus follow-up offered 1 or 3 years later for those with previous normal or unconfirmed abnormal BeLPT [c]CBD included 12 with "probable" CBD (7—no granulomas, 5—no biopsy during bronchoscopy); granulomatous CBD = 0.4% (17/4397) [d]Authors did not state how many BeS were evaluated with bronchoscopy
Stange et al. 2001 (62) Nuclear weapons facility	5173	235 (4.5)	81 (1.6)	[a]same facility as (29), (31) and (60); included current and former workers; data included results from (60); study involved initial testing plus follow-up offered 3 years later for those with previous normal or unconfirmed abnormal BeLPT [c]CBD may have included some with "probable" CBD (unclear) [d]authors did not state how many BeS were evaluated with bronchoscopy
Newman et al. 2001 (44) Precision machining	235	22 (9.4)	13 (5.5)	[a]included current and daily contract workers; study involved initial testing plus up to 2 rounds of biennial follow-up testing [b]all BeLPTs conducted at a single laboratory [d]86% of BeS (19/22) were clinically evaluated

[a]Number who participated in survey, including BeLPT. See Comments for notes about study population.
[b]BeS = beryllium sensitization; includes those also diagnosed with CBD. See Comments for studies where sensitization was not based on two or more (i.e., confirmed) abnormal BeLPTs.
[c]CBD: chronic beryllium disease. See Comments for studies where disease diagnosis was not based on granulomas in biopsy samples and/or other pathologic abnormalities consistent with CBD, or where CBD was diagnosed subsequent to radiographic abnormalities or symptoms.
[d]See Comments for percentage of BeS who were clinically evaluated for CBD using BALLPT and transbronchial biopsy subsequent to BeS; alternatives noted.

2) Medline Search Terms

1. beryllium.mp. or exp Beryllium
2. berylliosis.mp. or exp Berylliosis
3. 1 or 2 combined with the rest of the search terms as below in turn
4. urin*.mp. or exp Urinalysis/
5. exp Radiography, Thoracic/ or chest x-ray.mp.
6. chest xray.mp.
7. CXR.mp.
8. 8 or 6 or 7
9. exp Population Surveillance/ or surveillance.mp.
10. screening.mp.
11. lymphocyte proliferation test.mp.
12. exp Granuloma/ or exp Sarcoidosis/ or sarcoid*.mp.
13. exp Granuloma, Respiratory Tract/ or granuloma*.mp.
14. exp Granulomatous Disease, Chronic/ or granulomatous.mp.
15. pulmonary function test.mp. or Respiratory Function Tests/

3) Other Databases Searched by HSE infocentre

1. British Nursing Index
2. Embase
3. British Library's Inside Conferences and Conference Papers Index
4. SIGLE
5. CINAHL
6. Cochrane Library
7. Healsafe
8. Oshrom (5 OHS databases: HSELINE, NIOSHTIC, CISDOC, RILOSH, OSHLINE)

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Beryllium

A review of the health effects and the evidence for screening or surveillance in workers exposed to beryllium

As exposure limits for beryllium have decreased, so has the incidence and severity of chronic beryllium disease.

There are however an emerging number of cases of subclinical disease and beryllium sensitization (BeS) that are being detected with new immunological tests, namely the beryllium lymphocyte proliferation test (BeLPT). Almost all the recent data on screening beryllium workers relates to the BeLPT, and more traditional screening programmes such as spirometry and chest x-rays that have been in use since the 1950s have only been evaluated as secondary endpoints.

Whilst the BeLPT has revolutionised the diagnosis of chronic beryllium disease (CBD), concerns have been raised about its inter- and intra-laboratory variability, possible reversibility in patients and uncertain sensitivity and specificity. There is also debate about the natural history of BeS and subclinical CBD and the ethical aspects of identifying disease early when there is no treatment, and subsequent employment implications. Another issue for the UK is the fact that only one laboratory offers BeLPT testing, although certain evidence supports double sampling of tests across laboratories to improve sensitivity and specificity. All these factors have led to certain US based groups advocating the use of BeLPT for screening and others not.

Therefore, in the US, a definitive stance on the content of a health surveillance programme has not been possible from the current evidence base. This is supported by the fact, for example, that the National Institute for Occupational Safety and Health (NIOSH), whilst citing many articles on beryllium on its website, does not offer any specific advice on health surveillance in beryllium workers, as it does for other industries.

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