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Maeve G. MacMurdo, MBChB, Peggy M. Mroz, M.S.P.H, Daniel A. Culver, DO, Raed Dweik, MD, MBA, Lisa Maier, MD, MSPH, FCCP

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Title:

Chronic beryllium disease: update on a moving target

Maeve G MacMurdo, MBChB. Peggy M Mroz, M.S.P.H. Daniel A Culver DO. Raed Dweik, MD, MBA. Lisa Maier MD, MSPH, FCCP.

Abstract:
Beryllium exposure remains an ongoing occupational health concern for workers worldwide. Since the initial Occupational Safety and Health Administration (OSHA) ruling on a permissible exposure limit (PEL) for beryllium in 1971, our understanding of the risks of beryllium sensitization and chronic beryllium disease has evolved significantly. A new OSHA ruling released in early 2017 and implemented in late 2018 substantially reduced the PEL for beryllium, increased requirements for medical screening and monitoring and may ultimately enhance worker protection.

This review highlights advances in our understanding of the pathway from beryllium exposure, to sensitization and progression to chronic beryllium disease that guided the development of this OSHA ruling. Screening beryllium exposed workers and management of chronic beryllium disease will also be discussed. Finally, we will discuss the role of beryllium as a cause of morbidity and mortality among exposed workers in this potentially preventable occupational lung disease.

Forty years after the first beryllium exposure ruling, the Occupational Safety and Health Administration (OSHA) has released an updated ruling on allowable beryllium exposure within the workplace. Initially announced in 2017 as a final rule, enforcement of new, lower exposure limits began in late 2018. The new final rule for general industry significantly reduces permissible beryllium exposure limits, while increasing requirements for worker screening, and expanding the beryllium rule to the construction and shipyard industries.

Beryllium has been processed in the United States since the early 1930s, when the utility of beryllium in aerospace and weapons manufacture was first recognized. The US remains the largest manufacturer and exporter of beryllium to the global market., (Table 1).[1–3] In addition to primary beryllium processing, secondary use of beryllium alloys is widespread across a number of industries globally. (Table 2) An older article estimated at least 134,000 current US workers are directly exposed to beryllium, although definitive numbers are unknown; others have estimated a much higher number of workers directly exposed to beryllium. In addition, many more are likely to be exposed indirectly.[4]

The hazards of beryllium exposure are well documented and began to appear soon after beryllium was used in industrial applications. Van Ordstrand and colleagues at the Cleveland Clinic reported the first cases of beryllium toxicity in 1943 after noting acute, severe pneumonitis in workers at a beryllium processing factory.[5] At the same time, clusters of granulomatous lung disease dubbed “Salem Sarcoid” were reported in workers in fluorescent light manufacturing throughout Massachusetts.[6] These cases would subsequently become the first documented cases of chronic beryllium disease (CBD) in the United States.[6]

Due to its unique chemical properties, beryllium was used widely in defense applications, from navigational applications and parts of marine engines to nuclear weapons applications and research in the Department of Energy. As the number of reported cases grew throughout the 1940s, the link with beryllium exposure became increasingly clear. The possibility of an occupational epidemic among its workers lead the Atomic Energy Commission to develop the first regulations on allowable beryllium exposure in 1949.[1,3] These regulations set a maximum allowable beryllium exposure per shift for individual workers and peak exposure limits, as well as placing restrictions on allowable factory emissions and environmental exposures.

At the time of these initial regulations evidence of what represented a ‘safe’ level of beryllium exposure was limited. The risk of acute beryllium pneumonitis was clearly related to the degree of beryllium exposure. This association was not clear in chronic beryllium disease, where there was seemingly no identifiable relation between exposure and risk or severity of subsequent disease. Additionally, a series of cases of CBD had been reported in communities surrounding beryllium plants, where daily exposure was presumably significantly lower than in a factory enviroment.[7,8]

The decision was made to set the maximum allowable workplace exposure to beryllium at a level of 2 $\mu g/m^3$ over an 8 hour time period with an ambient air emission restriction of 0.01 $\mu g/m^3$ averaged over a 30 day period.[7,8] Ultimately these levels were somewhat arbitrarily chosen, and guided partially by industrial feasibility.[3,9] While the epidemiologic evidence supporting these limits was weak, they effectively led to the eradication of acute beryllium pneumonitis among workers. For a time they also appeared to have impacted the risk of CBD. In 1971 these exposure limits were subsequently adopted by the newly constituted Occupational Safety and Health Administration (OSHA).[9,10]

Since the establishment of this initial regulation, our understanding of the pathogenesis, clinical impact and diagnosis of CBD has significantly progressed. It has become increasing clear that the previous

regulations did not adequately prevent beryllium associated morbidity and mortality, and that workers worldwide remained at risk.

Identification of at-risk workers

From the first case reports of CBD it was clear that unlike acute beryllium pneumonitis, risk of developing CBD does not follow a clear dose-response curve. [7,11–18] Latency between exposure and symptom onset, symptom severity and risk of progression is variable, even in cases where exposure history was similar. Due to this variability, options for workplace screening were problematic. The majority of early cases were identified only at the time of significant, symptomatic disease.

Our ability to identify patients with chronic beryllium disease advanced with the discovery that lymphocytes of patients with cutaneous sensitivity or a patch test response to beryllium salts reacted with beryllium sulfate *in vitro*- triggering a type IV hypersensitivity response.[19] A similar response was seen in the lymphocytes of those with known pulmonary berylliosis.[20,21] These discoveries led to the theory that beryllium sensitization was a key step in the pathway towards chronic beryllium disease. A logical step forward was the use of lymphocyte proliferation testing (LPT) as a mechanism to identify workers early in the disease course.

In the 1980s the methodology underlying LPT testing was further refined, significantly improving sensitivity and accuracy. With these adjustments, the blood beryllium lymphocyte proliferation test (BeLPT) proved more accurate in identifying CBD across a number of cohorts. These initial studies lead to the realization that beryllium sensitization and CBD remained prevalent among beryllium exposed workers, despite the industrial standards of the time.[15,22,23]

The use of the blood BeLPT has become standardized as a mechanism for screening and diagnosis of beryllium sensitization and chronic beryllium disease. However, several important limitations of testing remain. The sensitivity of a single abnormal BeLPT remains relatively low (between 66-88%), though increases with repeat testing.[24–27] The test itself is performed in a limited number of laboratories across the country, and inter-laboratory definitions of what constitutes an abnormal test may vary.[28,29]

Whether workers with one abnormal BeLPT and subsequent normal tests without other clinical abnormalities, require more intensive screening going forward, or are at higher risk for subsequent progression to confirmed beryllium sensitivity has yet to be determined. In these patients, bronchoalveolar lavage (BAL) cell LPT testing in addition to transbronchial biopsies may be considered if suspicion for disease is high. BAL BeLPT is more specific than blood LPT testing. A single positive LPT from BAL cells is enough to confirm a diagnosis of beryllium sensitization (BeS).[30–32]

Beryllium Sensitization

The process of beryllium disease begins with the development of a CD4+ T cell immune response after exposure. Beryllium-specific CD4+ T cells are activated by engagement of a surface T-cell receptor with an MHC class II molecule on the surface of antigen presenting cells. An HLA-DPB1 gene on chromosome 6 with a glutamic acid residue at position 69 (E69) of the β-chain is highly associated with CBD and BeS. This gene is functional as demonstrated by blocking the HLA-DPB1 with an antibody which diminished proliferation and cytokine production in response to beryllium.

Once stimulated with beryllium via HLA-DP1, T cells proliferate in an oligoclonal manner, with release of IL-2, tumor necrosis factor-alpha (TNF) and interferon-γ which drive the process of granuloma formation

(Figure 1).[33,34] Sensitization is a necessary prerequisite for the development of CBD, and can be detected immediately, or decades after initial beryllium exposure.

The prevalence of BeS in exposed workers is variable, ranging from 1-16% across workplace cohorts (Figure 2).[14,16,35–40] While the risk of beryllium sensitization is present at any exposure level, increasing beryllium exposure has been associated with an increased risk of progression to CBD.[41] In particular machinists (workers who directly shape beryllium metal and alloys) appear to be at higher risk of developing both BeS and CBD when compared to other beryllium-exposed workers.[14,16,39] This may be due to higher exposure to beryllium as well as exposure to small respirable particles capable of reaching the distal airway and alveoli.

The amount and type of exposure is not the only relevant variable in risk of CBD. Not all machinists develop beryllium sensitivity, even when followed over decades. Furthermore, BeS and CBD has been identified in security guards, secretaries, accountants and spouses of beryllium workers, whose exposure levels were significantly lower. BeS and CBD have also been identified in cohorts of patients living near beryllium production facilities- supporting the theory that even limited exposure to beryllium can trigger clinically significant disease in susceptible individuals.[15,16,42]

Part of the missing link in the relationship between beryllium exposure and progression to sensitization appears to be genetic. Innate variability in major histocompatibility complexes (MHC) impacts the ability of an antigen presenting cell (APC) to respond to beryllium. Beryllium is especially able to bind HLA DPB1 E69 variants, changing the conformation of the peptide binding groove. This altered confirmation facilitates binding of self-peptide.[43] Once bound, the APC presents the antigenic compound (with beryllium buried in the cleft and not directly bound by the T-cell receptor) to CD4+ T cells, triggering a hypersensitivity/autoimmune like-response.[44–46]

Variation in the HLA-DPB1 E69 allele is the major factor in this immune response, as noted above. The presence of any DPB1 E69 allele is associated with a significantly increased risk of developing CBD.[46] Later studies also show an association between E69 and development of BeS.[45,47–49] The type of E69 modifies the risk of CBD and BeS, with the non-0201 variants conferring greater risk compared to the 0201 variants. The presence of two E69 alleles further increases the risk of both sensitization, and of CBD development.[41]

The risk of beryllium sensitization is ultimately multifactorial. Just as not all machinists develop beryllium sensitization, not all workers with beryllium exposure and an E69-possesing variant develop beryllium sensitization. Further, not all patients with diagnosed beryllium sensitization have a known HLA mutation. It is increasingly clear that workers who have more prolonged and or higher average exposure to beryllium, and higher task related exposures are more likely to develop chronic beryllium disease.[37,40,44,50] The presence of an E69 containing HLA allele further increases this risk.

Diagnosis of Chronic Beryllium Disease

The development of the BeLPT and initiation of workplace screening has substantially altered the natural history of CBD. When first described in the late 1940s, the vast majority of patients with CBD were symptomatic at time of diagnosis, presenting with dyspnea, weight loss and fatigue even if found based on chest radiographic screening.[51,52] Progression to end-stage respiratory failure was common, and pulmonary function test abnormalities were often present at time of first diagnosis.[51–54] Since the initiation of workplace screening the majority of patients diagnosed with CBD are minimally symptomatic at time of diagnosis.[37,55,56]

The diagnosis of CBD requires two criteria. Patients must have a confirmed history of beryllium sensitization- defined as two or more abnormal BeLPTS, at least one abnormal and one borderline BeLPT, or three borderline BeLPTs. Non-necrotizing granulomatous disease on lung biopsy, a positive BAL BeLPT with lavage showing a lymphocytosis of > 15% (consistent with granulomatous inflammation), or other compatible pathology must also be present.[2,32,57] Occasionally if imaging and exposure history are strongly suggestive a diagnosis of probable CBD can be made on imaging findings and positive BeLPT testing alone.[32] However, given the variability of imaging findings, most patient will require transbronchial biopsy to confirm the diagnosis.

While chest x-ray screening was used historically, imaging findings are often not present early in the disease course. With time, diffuse or upper lobe predominant reticulonodular densities may develop on chest x-ray. Computerized Tomography (CT) chest imaging is typically characterized by micronodular densities, ground glass opacification and occasionally areas of fibrosis.(Figure 3)[58] Hilar lymphadenopathy is a common feature, and may be the only imaging finding.[58]

Pulmonary function testing has not proved a reliable screening tool for CBD, and may be normal at the time of initial CBD diagnosis.[32] With time, obstructive, restrictive or mixed defects can manifest, although these findings are not specific for CBD.[59] Impaired gas exchange during cardiopulmonary exercise testing is one of the earliest clinical indications of chronic beryllium disease, and may be seen prior to the onset of clinical symptoms.[60]

The non-necrotizing granulomas of CBD consist of an aggregate of epithelial histiocytes with a collar of CD4+ T cells, and may be identical to those seen in sarcoidosis. Given the similarities in symptoms, imaging findings and pathology, misdiagnosis of sarcoidosis in patients with CBD may occur.[18,42] In patients with a diagnosis of sarcoidosis and a suggestive occupational history, BeLPT testing should be performed. Unlike sarcoidosis, extra-pulmonary CBD is relatively uncommon, though occasional cardiac and hepatic involvement were noted in early case series.[53]

Progression and treatment

Progression of disease in patients with CBD varies widely. Early data from the United Kingdom and United States beryllium registries suggested a mortality rate of approximately 30%, primarily due to progressive respiratory failure.[51,53,54] More recent longitudinal studies have suggested that roughly 20% of patients with a diagnosis of CBD will develop worsening respiratory symptoms requiring treatment initiation.[55,61] Even without worsening clinical symptoms, the majority of patients will experience deterioration in lung function over time.[17,55,61]

The pattern of decline within CBD patients is variable, including steady gradual deterioration, bursts of worsening symptoms followed by periods of stability, or minimal to no deterioration following initial diagnosis. The decision to initiate treatment for CBD is based on the rate and pattern of this decline and or presence of severe debilitating symptoms.[32]

Data supporting treatment of CBD are limited, though early treatment with inhaled corticosteroids has shown improvement in cough and shortness of breath, especially in patients with low FEV1 or RV.[62] Corticosteroid therapy is conventionally used as first line therapy, and is typically initiated at the time of symptom development or at clinical evidence of disease progression.[63] Prednisone is typically started at a dose of 20-40 mg, then slowly tapered, similar to initial treatment of sarcoidosis.[63] The majority of patients will experience improvement with steroid therapy, although this initial benefit may not persist.[64–66] Long

term response to steroids is more variable. A significant subset of patients will experience progressive deterioration even with ongoing therapy.[53,64,65]

Given the pathologic similarities to sarcoidosis, steroid sparing agents are used in those patients who fail to respond to first line therapy. While the data to support their use are limited, the harms of steroid therapy are well known. Steroid sparing agents should be considered in patients with progressive disease, or those requiring high dose corticosteroid therapy.[32,63,67] Infliximab was shown to affect the pulmonary immune response, improve quality of life measures and have its greatest impact on those with a low DLCO in a small clinical trial.[68]

The role that avoidance of further beryllium exposure plays in preventing disease progression remains unclear. OSHA mandates that workers diagnosed with beryllium related disease can request to be removed from further beryllium exposure. However, CBD develops in response to an altered pattern of immunity, triggered by beryllium exposure. Given this, it is likely that many patients will experience progression, even if they have no further direct exposure.

A New Era for Chronic Beryllium Disease

Over the last 30 years, it became increasingly apparent that the previous OSHA standard for beryllium exposure ameliorated, but did not prevent, the development of beryllium related disease. The vast majority of cases of CBD and beryllium sensitivity are diagnosed in workers whose level of exposure to beryllium is significantly below the previous upper limit of 2.0 $\mu g/m^3$ of air.[11,13,15] Additionally, cases of CBD in residents surrounding beryllium processing facilities continue to be detected.[7,18] These community cases appear to have developed secondary to ambient environmental exposure rather than secondary exposure from a family member or through indirect contact, since exposure occurred after the initial Atomic Energy Commission ruling.[18]

Increasing public concern about the risk of beryllium exposure prompted reassessment of the 2 $\mu g/m^3$ OSHA standard set in place in 1971. In 2015 OSHA began work on a new standard for beryllium. As of December 2018, a new OSHA permissible exposure level (PEL) of 0.2 ug/m^3, action level of 0.1 ug/m^3 and short term exposure limit of 2.0 ug/m^3 are now in effect, although clarifications and changes are still being addressed.[69] This ruling consists of reductions to the exposure limits as well as a requirement for medical screening provisions for workers anticipated to be exposed above the action level for 30 or more days per year. Major changes between the prior and new standard are highlighted in table 3.[69] Primarily, the new final rule substantially reduces the PEL to beryllium over an 8 hour period, from 2 $\mu g/m^3$ to 0.2 $\mu g/m^3$.[69] No changes have been made to the existing standard for beryllium emissions.

As with the previous ruling, the current PEL was chosen with the understanding that beryllium sensitization can occur at any level of exposure, but that further reduction in exposure should limit cases of CBD. Avoidance of higher level exposures may further reduce the risk of developing beryllium related disease, but will not fully eliminate it.[7,15,16,18,42]

Industrial hygiene measures and consistent use of personal protective equipment (PPE) have been shown to be effective in reducing rates of beryllium sensitization, and decrease the possibility of sensitization from dermal exposure.[70] The final rule requires increased engineering control over beryllium exposure- mandating enforcement of a ‘beryllium area’ and “regulated areas’ and increases the requirements for personal protective equipment (PPE) availability. Of note, these requirements do not extend across all beryllium-using industries. Shipyard and construction industries may be exempt from the provisions of the general industry rule, though legislation specific to these industries is in development.

Perhaps most importantly for the general pulmonologist, the final rule sets into place increased requirements for medical screening in workers at risk for beryllium exposure.[71] At the same time, it broadens the acceptable locations for beryllium screening, removing the requirement for the presence of an on-site laboratory capable of running BeLPT testing. While the majority of patients with beryllium exposure will likely continue to be seen at beryllium disease centers, as need for screening increases, more cases may be seen outside of this traditional framework.

The provisions outlined by the updated final rule represent a major step forward in the prevention of beryllium related morbidity and mortality. OSHA estimates that through increased regulation, 46 cases of chronic beryllium disease may be prevented each year, with significant healthcare cost savings.[72] However there remains no true 'safe' level of beryllium exposure. As long as beryllium is used in industry, cases of beryllium sensitization and chronic beryllium disease will continue to occur.

Summary

Beryllium remains in use across a number of industries in the United States, some of which are known to have beryllium exposure and some which may be poorly recognized as sources of exposure to workers. While the enhanced OSHA regulations may reduce beryllium exposure, they will not eradicate the risk of beryllium sensitization, or progression to chronic beryllium disease. With new requirements for medical screening, we are likely to see an increase in the frequency of diagnosis of beryllium sensitization and chronic beryllium disease. With that increased recognition, the questions of prognosis, treatment and disease prevention become increasingly pressing.

There remain gaps in our understanding of CBD and beryllium sensitization, particularly in the prediction of which workers will develop beryllium sensitization. The role of high risk genotypes and genetic screening for at risk worker groups has yet to be fully explored, and has significant ethical implications.[73] Furthermore, genetic screening is currently prohibited due to the Genetic Information Nondiscrimination Act of 2008 (GINA).[74]

Finally, while the OSHA final ruling mandates screening for workers who are actively exposed to beryllium, there is no requirement for screening of workers or contract workers with past exposure, including former workers. Given the known latency between exposure, sensitization and progression to chronic beryllium disease, the timing and length of post-exposure screening should be further explored.

The initial 1949 Atomic Energy Commission ruling to limit beryllium exposure was an important step towards reducing beryllium associated morbidity and mortality. Since that time, our understanding of the pathophysiology and progression of beryllium sensitization and chronic beryllium disease has significantly progressed. The OSHA final rule on allowable beryllium exposure reflects decades of research into this challenging condition. It will further reduce the incidence of beryllium sensitization and chronic beryllium disease, and increased detection of prevalent disease. However just as the initial 1949 ruling, the stricter limits on beryllium exposure continue to leave some workers at risk.

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TABLES:

Table 1: Major United States Beryllium Export Markets[75]

United States Beryllium Export Markets ($)
Germany (10.35 million)
Japan (4.57 million)
Malaysia (3.05 million)
United Kingdom (3.02 million)
China (2.79 million)
Canada (1.86 million)
South Korea (1.59 million)
Singapore (1.59 million)
Kazakhstan (1.59 million)

Table 2: Industries utilizing beryllium in the workplace

Industries at risk for beryllium exposure
Primary beryllium and alloy production
Dental labs
Aircraft and Aerospace manufacturing
Automotive manufacturing
Mining
Nuclear energy
Electronics and Optics
Plastic mould machining
Computer components manufacturing
Natural gas extraction
Telecommunications
Nuclear weapons development
Construction
Ceramic manufacturing
Abrasive blasting
Electronic recycling or refurbishment

Table 3: Comparison of key differences between the 1971 and 2017 OSHA final ruling on allowable beryllium exposure

	1971 final rule	**2017 final rule**
Permissible exposure limit/shift	2.0 micrograms per cubic meter of air, averaged over 8-hours.	0.2 micrograms per cubic meter of air, averaged over 8-hours.
Permissible short-term exposure limit	25.0 micrograms per cubic meter of air over a 30 minute sampling period.	2.0 micrograms per cubic meter of air, over a 15-minute sampling period.
Additional industries that may be covered	N/A	Construction workers, shipyards.
PPE requirements	No specific PPE requirement	Appropriate PPE must be provided- including skin protection, eye protection and a powered air-purifying respirator or negative pressure respirator
Workers requiring Screening	N/A	Every worker exposed to 0.1 µg/ m3 of beryllium for more than 30 days per year
Frequency of Screening	N/A	**At least** once every two years

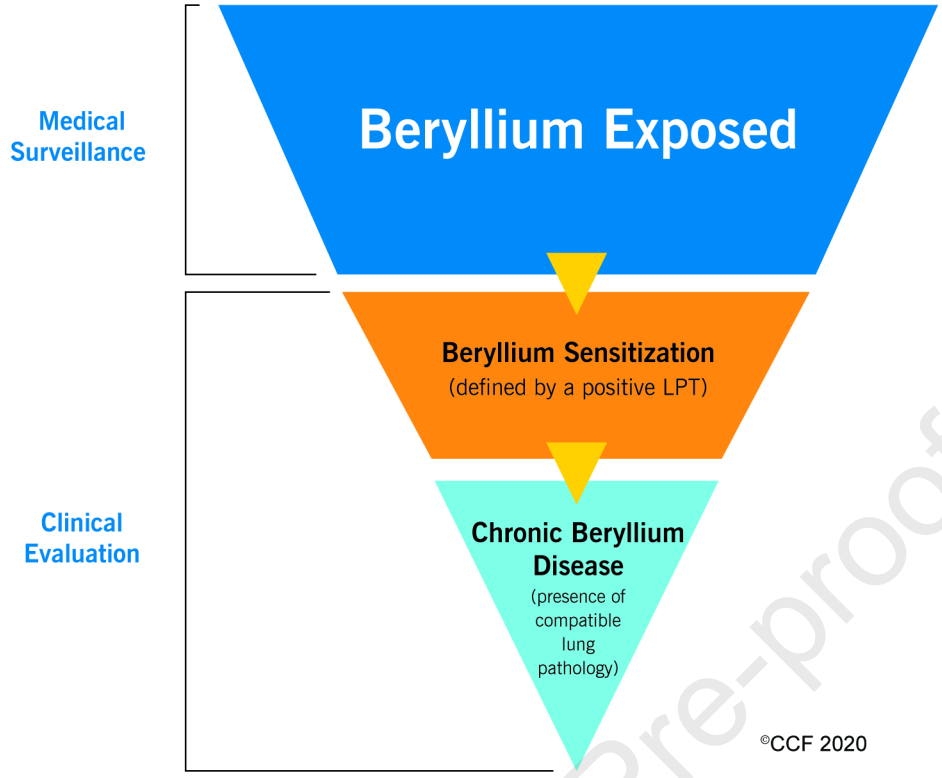
Figure 1:
The pathway from beryllium exposure to the development of chronic beryllium disease.

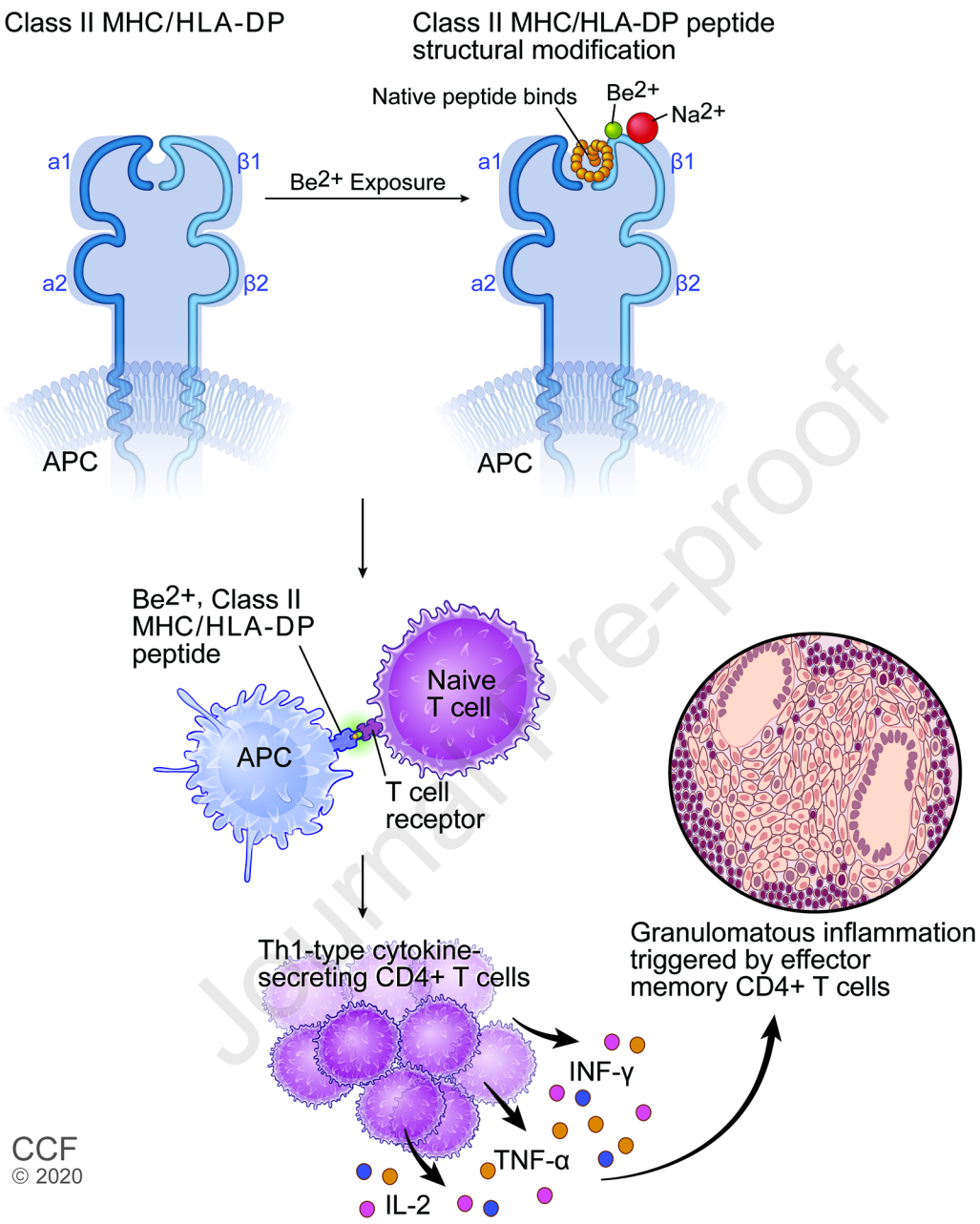
Exposure to beryllium results in alteration of an HLA-DPB1 E69 MHC configuration, allowing the MHC to bind self-peptide separate from the beryllium molecule itself. A self-peptide is presented to CD4 +ve T cells, leading to release of inflammatory cytokines, and the development of granulomatous inflammation.

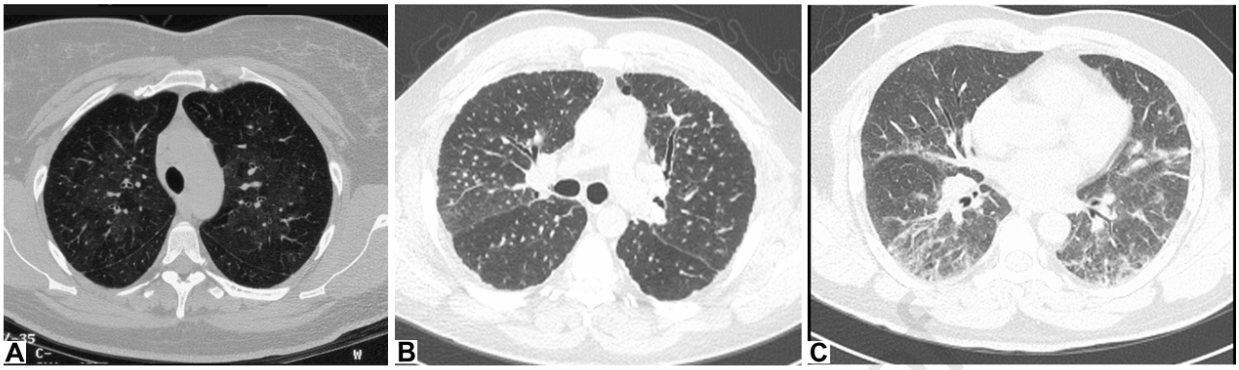
Figure 2:
Step-wise progression from beryllium exposure to chronic beryllium disease

Between 134,000-800,000 workers are exposed to beryllium in the workplace within the United States.[12,76] *By workplace, between about 1% to 18% of those exposed to beryllium develop beryllium sensitization. 6-8% of workers with beryllium sensitization will progress to chronic beryllium disease per year.*[55] *Between 15-100% of workers with beryllium sensitization will have Chronic Beryllium Disease at the time of sensitization diagnosis.*[15,16]

Figure 3:
CT images highlighting the spectrum of imaging abnormalities in chronic beryllium disease, ranging from ground glass opacification (A), disseminated nodular opacities (B) and ground glass opacification with septal thickening and fibrosis (C).







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Maeve G MacMurdo MBChB- Cleveland Clinic Respiratory Institute. macmurm@ccf.org
Peggy M Mroz, M.S.P.H. National Jewish Health, Division of Environmental and Occupational Health Sciences mrozp@njhealth.org
Daniel A Culver DO. Cleveland Clinic Respiratory Institute. Cuvlerd@ccf.org
Raed Dweik, MD, MBA. Cleveland Clinic Respiratory Institute. dweikr@ccf.org
Lisa Maier MD, MSPH, FCCP. National Jewish Health, Division of Environmental and Occupational Health Sciences. lisamaier@njhealth.org

Maeve G MacMurdo MBChB

9500 Euclid Avenue A90

Cleveland, OH

44195

macmurm@ccf.org

Correspondence to: Maeve G MacMurdo- macmurm@ccf.org

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