EDITORIAL

The Beryllium Occupational Exposure Limit: Historical Origin and Current Inadequacy

This report considers the historical origin of the current beryllium occupational exposure limit (OEL) and the evidence that led most authorities to conclude that it was adequately protective against clinically evident chronic beryllium disease (CBD). Nearly 40 years later, during the late 1980s, it was shown that in addition to CBD, beryllium can cause asymptomatic sensitization and asymptomatic ("subclinical") lung disease. It is now known that beryllium sensitization can progress to beryllium disease. Moreover, beryllium sensitization has been found in workers employed at facilities where exposures infrequently, if ever, exceeded the OEL. Historic beryllium exposure limits, which in their time seemed adequate to protect against clinically evident CBD, no longer seem sufficient.

There is considerable concern that current occupational exposure limits (OEL) provide insufficient protection for beryllium-exposed workers. The beryllium OEL, first proposed and adopted by the U.S. Atomic Energy Commission (AEC) in 1949[1,2] and subsequently adopted by virtually all advisory and regulatory agencies, has persisted with only minor changes despite major advances in our understanding of beryllium-induced disease and important changes in the diagnostic approach used for beryllium-affected workers.

Over the past decade, an increasing number of authorities have argued that the beryllium OEL should be lowered, but no changes have thus far been made. In 1996, Brush Wellman, the sole North American beryllium producer, expressed uncertainty that the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) was adequately protective.[3] The following year, the U.S. Department of Energy (DOE) published interim guidelines,[4] with final regulations published in 1999,[5] for a Beryllium Disease Prevention Program for workers at DOE sites, but DOE did not modify its OEL. Also in 1999, the American Conference of Governmental Industrial Hygienists (ACGIH) published a notice of intent to lower its threshold limit value (TLV) for beryllium,[6] but no changes have been made. OSHA, in 2002, published a Request for Information as a first step toward setting a new beryllium PEL,[7] but new values have yet to be proposed.

The origins of the beryllium OEL and its persistence for more than 55 years provide interesting perspectives on historic and current practices of occupational medicine and industrial hygiene. Both its origin and persistence can be understood in light of the evolving knowledge about chronic beryllium disease (CBD) and the development of increasingly advanced diagnostic methods.

Origins and Basis of the 2-$\mu g/m^3$ Beryllium Occupational Exposure Limit

Beryllium-related pneumonitis was first described in Germany and Russia during the 1930s[8] and in the United States in the early 1940s.[9,10] The etiology of disease was not known, but early researchers and the U.S. Public Health Service[11] blamed exposure on airborne acid anions (eg, fluorides and sulfates) from beryllium smelting rather than beryllium itself. The first clear association between beryllium exposure and the disease now known as CBD was a 1946 report by Hardy and Tabershaw that described chronic lung disease in fluorescent light bulb workers.[12] That publication, followed by a 1947 Saranac Lake symposium,[13] initiated a variety of beryllium-related research efforts largely sponsored by AEC.

Efforts to establish an appropriate OEL were led by the Director of the AEC Health and Safety Laboratory, Merrill Eisenbud. In 1949, after 2 years of study, AEC adopted an OEL of 2 $\mu g/m^3$ as a daily weighted average (DWA).[1]* Because there was no epidemiologic basis for setting an exposure limit, the recommendation was based on an analogy between beryllium and other toxic metals: "Start with the assumption that beryllium was as toxic as some of the heavy metals, such as arsenic, lead, and mercury. However, since the heavy metals have atomic weights of about 200, and since beryllium has an anatomic weight of 9, the TLV would have to be reduced by a factor of about 20 relative to the heavy metals . . . when corrected for differences in molarity, the TLV for beryllium would be about 5 $\mu g/m^3$."[1]

Because of concerns about the severity and reversibility of CBD, an additional safety factor was recom-

*Unlike more familiar time-weighted averages (TWA), which measure the "average exposure for an individual over a given working period, as determined by sampling at given times during the period,"[66] DWAs calculate average exposures "using a formula incorporating average general area, full-shift area and breathing zone measurements based on time studies for most jobs."[62]

mended on a "tentative basis," thereby lowering the final recommended OEL to 2 μg/m^3.

As first promulgated, the OEL was intended to reflect exposures averaged from samples obtained over quarterly periods.[14] In addition to the OEL of 2 μg/m^3 DWA, AEC also proposed a ceiling exposure limit of 25 μg/m^3 and an ambient exposure limit of 0.01 μg/m^3.† Before adoption, these recommended exposure limits were reviewed and approved by an expert panel chaired by Harriet Hardy. By prior agreement, the OEL was reevaluated by the expert panel after 6 months and then annually.[1] Each time, the OEL was reaffirmed. The panel disbanded in 1958, concluding its work by recommending that "henceforth proper governmental and industrial agencies be encouraged to adopt maximum allowable concentrations for general publication."[15]

General Adoption of the 2-μg/m^3 Beryllium Occupational Exposure Limit

When first adopted, the beryllium OEL applied solely to AEC installations and AEC contractors. At that time, there were few beryllium-exposed U.S. workers not employed by AEC or its contractors; use of beryllium-containing phosphors in fluorescent bulbs had ceased by 1950. During the following years, however, use of beryllium spread to non-AEC worksites and occupational beryllium exposures became an issue for increasing numbers of workers not covered by the AEC standards. Accordingly, the two leading U.S. industrial hygiene organizations initiated efforts to establish more generalized occupational exposure limits for beryllium.

The American Conference of Governmental Industrial Hygienists (ACGIH) adopted a "tentative" 2-μg/m^3 OEL in 1955, proposed formal adoption of the 2-μg/m^3 OEL in 1957, and formally adopted it as a threshold limit value (TLV) in 1959.[16] Unlike the AEC standard, however, the ACGIH TLV applied to exposures averaged over an 8-hour workday, not over a quarterly period. By shortening the exposure averaging time, the ACGIH TLV effectively lowered the upper range of allowable worker exposures. On the other hand, ACGIH did not establish short-term or ceiling exposure limits.

In 1956, the American Industrial Hygiene Association (AIHA) also adopted 2 μg/m^3 OEL as a "tentative" hygienic standard.[17] Although describing its standard as "also the current recommendation of AEC," it applied to 8-hour exposures, not quarterly averaged samples as recommended by AEC. Like AEC, but unlike ACGIH, it included a 30-minute exposure ceiling of 25 μg/m^3. The AIHA hygienic standard for beryllium was formally adopted in 1964.[18]

In 1970, the American National Standards Institute (ANSI) also adopted 2 μg/m^3 as an 8-hour time-weighted average OEL for beryllium,[19] but the ANSI standard applied to particulate ≤5 μm in diameter; the standard applied to total dust samples only "if particle size cannot be determined." By adopting the 2 μg/m^3 for size-selected particulate, ANSI allowed significantly greater total exposures than were permitted under previous beryllium standards; the National Institute for Occupational Safety and Health (NIOSH) estimated that inclusion of only respirable particles eased the standard by as much as five- to tenfold.[15] A 30-minute exposure ceiling of 25 μg/m^3 was also adopted. ANSI also adopted an 8-hour ceiling limit of 5 μg/m^3 and a 30-minute peak exposure limit of 25 μg/m^3 for up to 30 minutes per day.

OSHA, in 1971, promulgated a beryllium PEL of 2 μg/m^3 for 8-hour time-weighted average exposures. Government records indicate that OSHA adopted the ANSI standard,[20] but unlike ANSI, the OSHA PEL applied to total particulate, not respirable samples, and OSHA did not adopt an exposure ceiling. Thus in practice, the OSHA PEL was equivalent to the ACGIH TLV and AIHA Hygienic Standard and set a more restrictive exposure limit than did the AEC, or ANSI standards.

Lastly, in 1972, NIOSH adopted 2 μg/m^3 as a recommended exposure limit (REL): "the standard recommended . . . is similar to that adopted by the AEC in 1949 and the present OSHA environmental standard."[15] Like the OSHA PEL, the REL applied to 8-hour time-weighted average exposures for breathing zone samples of total beryllium particulate,‡ but unlike OSHA, it included a 30-minute ceiling limit of 25 μg/m^3.

Thus, by 1972, occupational beryllium exposure limits of 2 μg/m^3 had been adopted by AEC, ACGIH, AIHA, ANSI, OSHA, and NIOSH. Despite specific differences in the details of those standards, there was agreement that 2 μg/m^3 was both feasible and adequately protective. That view was articulated by NIOSH in its 1972 criteria document[15]: "It is felt to be feasible technologically for the control of worker exposure to beryllium and effective biologically for protection of the worker from acute and chronic beryllium disease."

†The ambient limit reflected concerns that CBD occurred in people living near beryllium plants who were not occupationally exposed. Thirteen Ohio cases were reported in 1949[67,68] and 16 Pennsylvania cases were reported in 1959.[69,70] Dispersion modeling suggested that Ohio cases had been exposed 0.01–0.1 μg/m^3 beryllium[67]; exposures could not be reconstructed for the Pennsylvania cases. Apparently, the neighborhood cases were all exposed before 1950 and from 1950–1980, only one additional case was diagnosed near the Ohio plant.[26] These neighborhood cases have been cited as evidence that the OEL was inadequately protective.

‡As described in an Appendix to the 1972 NIOSH Criteria Document, the recommended REL was to be calculated as a DWA value that might reflect brief sampling periods. For example, quarterly exposure levels could be calculated by averaging only three 30-minute general area samples during "representative activity" and only three 3-minute breathing zone samples for "each operation."[15]

We now know, in light of current knowledge about beryllium-induced disease, that such statements reflected excessive confidence. Nevertheless, at that time, such views seemed justified. The reasons that so many well-informed physicians and scientists viewed the 2-μg/m^3 OEL as adequate, or even overly protective, are considered subsequently.

Apparent Efficacy of the 2-μg/m^3 Beryllium Occupational Exposure Limit

Implementation of the 2-μg/m^3 standard did not occur "overnight." To the contrary, many facilities required substantial modification to achieve compliance, a process that took years in some cases. It was probably 1960 or later before most facilities were able to achieve the standard, although that standard was still often exceeded.[14,15,20,21] Nevertheless, there was a widely shared sense that the new standard was effective.

In part, that view was based on reports from the Beryllium Case Registry, established in 1952 at the Massachusetts Institute of Technology and subsequently moved to the Massachusetts General Hospital and then NIOSH.[22–24] The Registry aimed to identify all known beryllium disease cases to study causation and treatment. Registry efforts were limited by the unknown size of at-risk populations, by limited occupational exposure data, and by failure to identify all new cases because reporting was voluntary,[23] but Registry data provided the most substantial body of information then available on beryllium disease. Beginning with approximately 300 known cases in 1951, the Registry grew to include 606 cases by 1958, 760 cases by 1966, and 888 cases by 1982 (at which time 45 other cases were known to exist but had not been reported).[23,25,26]

The Registry documented a "dramatic" reduction in the incidence of beryllium disease in workers hired after 1949. In 1959, a Registry report concluded: "It would appear that the controls which were introduced in 1949 have been effective."[25] The relative absence of cases among workers hired after implementation of exposure controls persisted for many years. Figure 1 illustrates the decline in diagnosed cases according to year of first exposure, whereas Figure 2 normalizes those new cases by the quantity of beryl ore mined, a measure of annual beryllium production.

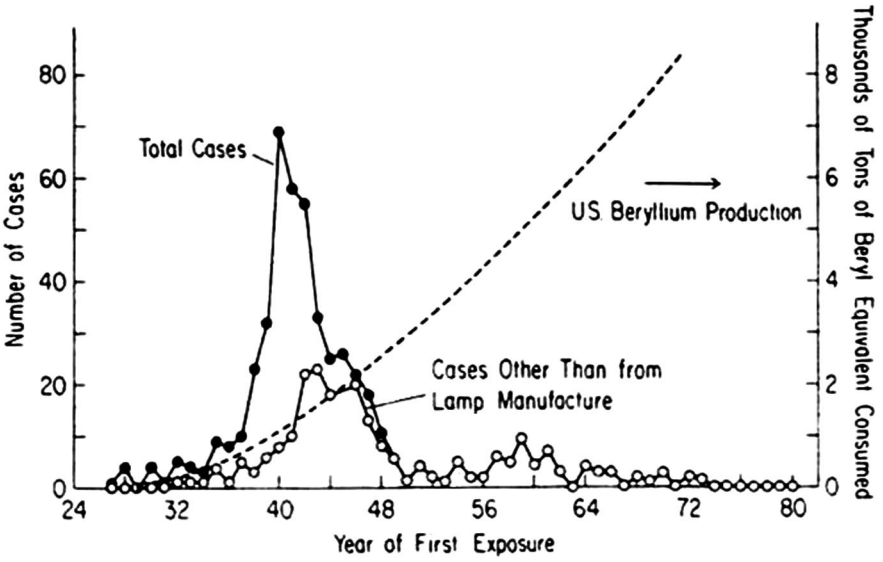

Fig. 1. Reported cases of work-related beryllium lung disease ("occupational berylliosis") by year of first exposure, 1927–1980, and annual U.S. beryllium consumption (thousands of tons of beryl equivalent). (Reprinted from Eisenbud M, Lisson J. Epidemiological aspects of beryllium-induced nonmalignant lung disease: a 30-year update. *J Occup Med.* 1983;25:196–202, with permission of the publisher.).

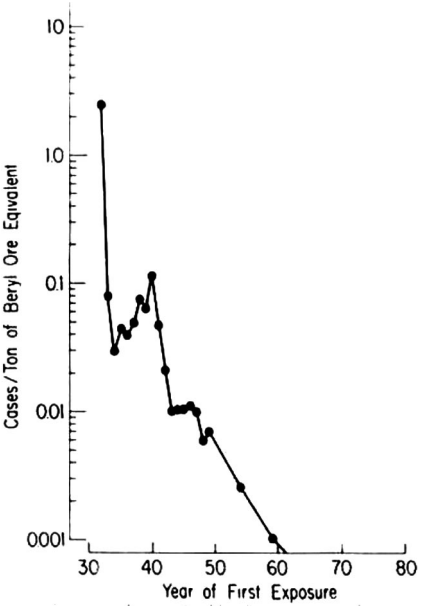

Fig. 2. Reported cases of work-related beryllium lung disease ("occupational berylliosis") by year of first exposure per ton of beryl ore consumed; incidence rates after 1960 are <0.001 cases/ton and are not plotted). (Reprinted from Eisenbud M, Lisson J. Epidemiological aspects of beryllium-induced nonmalignant lung disease: a 30-year update. *J Occup Med.* 1983;25:196–202, with permission of the publisher.).

Such data led many to applaud the 2-μg/m^3 standard. NIOSH (quoted previously) concluded in 1972 that that standard was "effective biologically for protection of the worker" from beryllium disease.[15] Likewise, summarizing Case Registry experience in 1980, Harriet Hardy found that "beryllium and its compounds can be handled safely . . . between 2 and 5 μg/m^3 for an eight hour day and a forty hour week."[27] In 1987, the Environmental Protection Agency endorsed the effectiveness of the standard: "No adverse effects have been noted in industries complying with the 2 μg/m^3 standard . . . therefore, it appears that this level of beryllium in air provides good protection with regard to respiratory effects."[28] As recently as 1993, the ATSDR Toxicology Profile for Beryllium noted the dramatic decrease

in CBD cases after implementation of exposure controls, thus "demonstrating the effectiveness of the implementation of the 2 μg/m^3 OSHA standard in controlling CBD."[29]

Supportive data also accumulated at DOE, successor agency to AEC. Although much DOE data were not openly published, the clinical experience of DOE workers at Oak Ridge National Laboratory and Rocky Flats nuclear facility were reviewed by the U.S. General Accounting Office in a 2000 report[20]: "From the 1970s through 1984, the incidence of CBD appeared to significantly decline at Energy facilities. This apparent reduction, along with the long latency period for the disease, led Energy to assume that CBD was occurring only among workers who had been exposed to high levels of beryllium decades earlier, such as in the 1940s."

Similar observations were made at Los Alamos National Laboratory: "By the early 1980s compliance with the 2 μg/m^3 OEL was believed to have prevented new cases of CBD."[30]

In addition to the U.S. experience, support for the 2-μg/m^3 standard was seen in the absence of CBD cases reported from the Cardiff beryllium facility in the United Kingdom. From 1961–1997, 367,757 area samples were obtained, along with 217,681 personal samples from 400 employed workers; only 0.1% of area samples and 0.5% of personal samples were >2 μg/m^3.[31] During its 38 years of operations, no worker developed CBD resulting from inhalation exposure.§

Thus, accumulated experience seemed to endorse the consensus 2-μg/m^3 OEL and with increasing time, that endorsement seemed stronger and stronger. However, not all reported studies were supportive.

Early Reports of Chronic Beryllium Disease at Exposures <2 μg/m^3

During the 1970s and 1980s, three research groups published reports suggesting that the 2-μg/m^3 beryllium OEL might not adequately protect workers from CBD. First, in a series of reports beginning in 1973, Shima and colleagues described 15 cases of CBD in Japanese beryllium workers at facilities where exposures were reported to be "much lower than 2 μg/m^3."[32–34] However, it seemed likely that Shima had significantly underestimated worker exposure.

One reason for doubting the conclusion of the Shima reports was that their exposure data had been obtained following then-standard Japanese industrial hygiene protocols that relied on area samplers placed geometrically throughout the work area, rather than in workers' breathing zones or specifically near high-exposure tasks.[35,36] Area samplers generally understate worker exposures and NIOSH studies had documented that area samples significantly underestimated the actual exposures of beryllium workers.[37] ‖Thus, it seemed almost certain that the workers had been exposed to higher levels than those reported by Shima. A second reason was that Shima also described 27 cases of acute beryllium pneumonitis among facility workers.[32,33] Because acute beryllium pneumonitis had been associated with only very high exposure levels (eg, >100 μg/m^3),[1,38] those cases indicated that facility exposures must have been substantially greater than 2 μg/m^3.

In 1983, Cotes et al described five English workers who developed CBD while working in a beryllium plant where estimated average exposures were said to have not exceeded 2 μg/m^3.[39] However, data presented in that report describe a different picture. The affected workers had been employed between 1952 and 1977, but exposure data were available only for 1952–1960 and some of that data were missing. Data gaps were filled by "guesses" and geometric mean exposure averages were "estimated by eye." Exposure levels were based on area samples, not personal samples, and therefore exposures were probably significantly higher. In addition, at least two of 206 plant workers had developed acute beryllium pneumonitis, an indication of very high exposure. Of available exposure data, 9% (318 of 3401) were >2 μg/m^3, 0.6% (20 of 3401) were >25 μg/m^3, and two exceeded 100 μg/m^3.

Further complicating the study was significant beryllium contamination that was found throughout the plant, particularly in nonproduction areas. Seventeen percent (28 of 168) of samples from the workers' dressing room, 11% (six of 54) from the plant laundry, and 3% (two of 73) from the plant laboratory were >2 μg/m^3. Based on these data, it seems certain that this plant was widely contaminated and that workers' exposures were greater than those estimated in the report. Thus, it is not surprising that the Cotes study had little impact on the 2-μg/m^3 standard.

In 1987, Cullen et al reported the diagnosis of CBD in five precious metal refinery workers with seemingly low exposures.[40] Four had worked in the furnace area between 1964 and 1977; the fifth worked from 1969 to 1983 in other refinery areas. Exposure data were limited to two 1-week surveys performed during 1983. Levels in the furnace area averaged <2 μg/m^3, but time-weighted average personal samples

§In 1963, CBD was diagnosed in a worker who had sustained a beryllium-contaminated finger laceration that ulcerated and progressed to require finger amputation. That individual developed chronic granulomatous disease involving his arm and lung.

‖There is also very little correlation between area and personal beryllium samples. In NIOSH studies, linear regression between personal total particulate samples and an AEC method using personal and area samples had an $R^2 < 0.25$.[37] In more recent DOE studies, no linear correlation was found between personal and area samples ($R^2 = 0.014$).[65]

throughout the plant ranged from 0.22 to 42.3 $\mu g/m^3$. Overall, 10% of samples were >2 $\mu g/m^3$ and levels outside the furnace area (where the affected workers were also exposed) were "often much higher than the standard."[40]

Although the study suggested that CBD had developed in workers apparently exposed below 2 $\mu g/m^3$, the authors described several considerations that raised doubts about their conclusion. First, the filter method for sample collections may have underestimated exposure levels near the furnaces "where beryllium is likely to be in the form of a fine fume, unlike the dust exposures elsewhere."[40] Additional concerns were the limited number of samples, that sampling was performed years after the workers had left the refinery, and the high levels seen outside the furnace area. In 1993, the ATSDR Toxicology Profile for Beryllium presented a similar list of concerns: "underestimation of exposure levels . . . measurement of levels only in 1983, although exposure occurred between 1964 and 1977; limited sampling, which . . . may have missed high concentrations; the possibility that the workers in question were also exposed to high levels . . . outside the furnace area."[29] Thus, this study was viewed as only suggestive, but uncertain proof that the 2-$\mu g/m^3$ beryllium standard was not protective.

These reports illustrate the difficulty of identifying workers known to have never been exposed to >2 $\mu g/m^3$ beryllium. Even very recent studies in low-exposure facilities have reported exposures greater than the OEL. For example, a 2005 study of copper–beryllium alloy workers included 650 personal and 815 short-duration high-volume (SDHV) breathing zone samples.[41] The median value for personal samples was 0.02 $\mu g/m^3$, but 1% exceeded the 2-$\mu g/m^3$ OEL. The median value for SDHV samples was 0.44 $\mu g/m^3$, but 10% were >5 $\mu g/m^3$ and 3% were >25 $\mu g/m^3$. Thus, the possibility of unrecognized high-level exposures could almost never be excluded.

Ultimately, a credible challenge to the beryllium standard was not possible until diagnostic methods had evolved to allow the recognition and characterization of subtle beryllium-induced effects that were clinically quite different from the disease then known as CBD.

The 'Modern Era' of Beryllium Disease

Formal diagnostic criteria for CBD were developed in the early 1950s as a basis for admitting cases to the Beryllium Case Registry. Those criteria, which remained the principal diagnostic criteria for nearly 40 years, addressed two concerns: "establishment of significant beryllium exposure" and "objective evidence of lower respiratory tract disease."[23] "Significant exposure" was determined on the basis of either: 1) occupational history and/or results of air samples or 2) the presence of beryllium in tissues or urine. Clinically "objective evidence" was defined as finding of at least two of the following: 1) clinical symptoms and course consistent with CBD; 2) characteristic histologic changes in lung tissue or lymph nodes; 3) chest x-ray evidence of interstitial fibronodular disease; or 4) decreased pulmonary function tests (obstruction or restriction and diminished diffusing capacity).[42,43] Thus, for nearly 40 years, CBD was diagnosed in only those with clinical symptomatic disease and accordingly, it was regarded as a disease of substantial morbidity and mortality.

That view of CBD changed during the late 1980s as a result of technologic advances that changed the criteria for CBD and "revolutionized"[44] the diagnostic approach to beryllium disease. One advance was the refinement of analytical methods for detecting beryllium-sensitized lymphocytes, a laboratory technique that has evolved for more than 30 years.[45–50] Another was the popularization of fiberoptic bronchoscopy. These advances led to a fundamentally different understanding of the natural history and epidemiology of beryllium-induced disease.

The immune nature of CBD was first proposed on the basis of epidemiologic observations;[2] subsequent laboratory research documented sensitized lymphocytes in patients with CBD, which proliferated in vitro when cultured with beryllium salts.[45,51–53] That led to in vitro lymphocyte proliferation tests (beryllium lymphocyte proliferation test [BeLPT]), used initially as a research tool in patients with known CBD.[40,46,47] By 1989, BeLPT (then known as the "lymphocyte transformation test") had not been "systematically applied in the evaluation of persons at risk."[54] Thus, it was not then known whether BeLPT could identify individuals with otherwise unrecognized (ie, asymptomatic) CBD.

The importance of fiberoptic bronchoscopy was the ease with which it allowed clinicians to perform bronchoalveolar lavage (BAL) and obtain lung tissue biopsies. During the 1980s, it was found that BAL lymphocytes were often more sensitive to beryllium-induced proliferation than blood lymphocytes, nearly always yielding positive results on proliferation testing in patients with clinical CBD.[48] Besides providing confirmation that CBD was a hypersensitivity disease, the combination of fiberoptic bronchoscopy, BAL, and BeLPT allowed physicians to diagnose beryllium-mediated disease in patients in whom a history of "significant beryllium exposure" could not be proven. The generally low morbidity of fiberoptic lung biopsies made it possible to look for the characteristic histologic changes of CBD in patients with positive BeLPT but no other indications of beryllium disease.

In a classic 1989 report, Newman and colleagues used BeLPT and fiberoptic bronchoscopy to diagnose CBD in 12 beryllium-exposed work-

ers, of whom five did not meet the Beryllium Case Registry criteria.[54] That led them to propose a 3-category classification system reflecting "the wider range of beryllium effects": 1) "beryllium disease" (equivalent to clinically evident CBD); 2) "subclinical beryllium disease" (abnormal BeLPT and characteristic lung biopsy, but no "constellation" of clinical findings); and 3) "beryllium sensitization" (abnormal BeLPT). Later that year, they reported the use of BeLPT and bronchoscopy to diagnose an additional four workers with "subclinical beryllium disease."[55] Thereafter, beryllium was recognized as causing a spectrum of effects, from asymptomatic sensitization to clinically evident disease.[44]

It is useful to note that traditional diagnostic tests were often normal in those identified as having subclinical beryllium disease or beryllium sensitization. For example, among four cases of subclinical disease reported by Kreiss et al,[55] none had sought medical attention, none had abnormal forced vital capacity (FVC), or abnormal forced expiratory volume in 1 second (FEV_1), and only one had an abnormal chest x-ray. Likewise, among 12 beryllium-exposed workers diagnosed by BeLPT and bronchoscopy as having subclinical beryllium disease or beryllium sensitization, only five had sought medical attention, whereas nine had normal pulmonary function tests, 11 had normal lung diffusion (DL_{CO}), and five had normal chest x-rays.[54] It was clear, therefore, that "subclinical beryllium disease" was clinically very different from the often grave, disabling disease described in reports of the Beryllium Case Registry.[56]

As these new diagnostic criteria were implemented, it became evident that two important aspects of beryllium disease required study. One concerned the natural history of beryllium sensitization and subclinical beryllium disease. Progression from "beryllium sensitization" to "beryllium disease" (defined as the presence of characteristic histologic changes) has been documented in a number of cases,[57–59] but only one relatively small longitudinal study (55 subjects) has specifically addressed disease progression in beryllium-sensitized workers.[60] Whether and how often such progression leads to "clinically manifest disease" have yet to be determined.[61] Thus, the natural history and rate of progression from beryllium sensitization to clinically evident CBD is still unknown.

The second aspect concerned the level of exposure necessary to induce the various forms of beryllium disease. Early studies (reviewed here) provided evidence that CBD (as defined by Case Registry criteria) rarely or never occurred in workers unless they had been exposed to beryllium levels >2 $\mu g/m^3$. Since 1989, however, "beryllium sensitization" and "subclinical beryllium disease" have been reported in workers at facilities where that level was only infrequently, if ever exceeded.[41,62–65]

In light of such findings, it seems that the current 2-$\mu g/m^3$ OEL provides insufficient protection for beryllium-exposed workers. The certainty of such conclusions, however, is necessarily limited because few workers have been continuously monitored, most studies have been based on relatively small numbers of personal breathing zone samples, and occasional peak exposures may be more critical to beryllium sensitization and disease than are lower long-term mean exposures. It is wise to observe the cautions voiced by Kreiss and colleagues about beryllium workplace studies: "Considerable uncertainty surrounds any reconstruction of past exposures."[62]

Conclusion

Our understanding of beryllium-induced sensitization and beryllium lung disease has fundamentally changed over the past 50 years. Over the same time period, implementation of exposure controls and reduction of workplace exposures dramatically changed the clinical presentation of beryllium-affected workers. The rapidly progressive, often fatal disease described in 1946 has essentially disappeared, replaced by a more indolent syndrome and a premorbid state of lymphocyte sensitization. Although the natural history of beryllium sensitization is uncertain, that it can progress to beryllium disease justifies adoption of more restrictive exposure standards. Historic standards, which in their time seemed adequate to protect against CBD, no longer seem sufficient.

Acknowledgment

This study was supported by Brush-Wellman Company.

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References

1. Eisenbud M. Origins of the standards for control of beryllium disease (1947–1949). *Environ Res*. 1982;27:79–88.
2. Sterner JH, Eisenbud M. Epidemiology of beryllium intoxication. *Arch Ind Hyg Occup Med*. 1951;4:123–151.
3. Brush Wellman Engineered Materials. Statement of Current Knowledge on Chronic Beryllium Disease (August 1996). Available at: http://www.brushwellman.com/EHS/BHS/08-96%20H&S%20Update.pdf. Accessed November 4, 1996.
4. Office of Worker Health and Safety. *Implementation Guide: Interim Chronic Beryllium Disease Prevention Program (DOE G 440.1–7).* Washington, DC: US Department of Energy; 1998.
5. Department of Energy. Chronic Beryllium Disease Prevention Program; Final Rule. *Fed Reg.* 1999;64:68854–68914.
6. *Threshold Limit Values for Chemical Substances and Physical Agents Biological Exposure Indices (BEIs*). Cincinnati:: American Conference of Governmental Industrial Hygienists; 1999.
7. OSHA. *Unified Agenda Prerule Stage 1218-AB76-1973. Occupational Exposure to Beryllium.* Washington, DC: US Department of Labor; 1973.
8. Gelman I. Poisoning by vapors of beryl-

lium oxyfluoride. *J Ind Hyg Toxicol*. 1936;18:371–379.
9. Van Ordstrand HS, Hughes R, Carmody MG. Chemical pneumonia in workers extracting beryllium oxide. *Cleve Clin Quart*. 1943;10:10–18.
10. Van Ordstrand HS, Hughes R, DeNardi JM, Carmody MG. Beryllium poisoning. *JAMA*. 1945;129:1084–1090.
11. Hyslop F, Palmes ED, Alford WC, Monaco AR, Fairhall LT. *The Toxicology of Beryllium (US Public Health Service Bulletin 181).* Washington, DC: US Public Health Service; 1943.
12. Hardy HL, Tabershaw IR. Delayed chemical pneumonitis occurring in workers exposed to beryllium compounds. *J Ind Hyg Toxicol*. 1946;28:197–211.
13. *Pneumoconiosis: Beryllium, Bauxite Fumes, Compensation (Sixth Saranac Symposium*). New York: Paul Hoeber; 1950.
14. Eisenbud M. The standard for control of chronic beryllium disease. *Appl Occup Environ Hyg*. 1998;13:25–31.
15. National Institute for Occupational Safety and Health. *Criteria for a Recommended Standard. Occupational Exposure to Beryllium.* Washington, DC: US Department of Health, Education and Welfare; 1972.
16. American Conference of Governmental Industrial Hygienists. *Documentation of the TLVs and BEIs with other Worldwide Occupational Exposure Values.* Cincinnati: ACGIH; 2002.
17. American Industrial Hygiene Association. *Hygienic Guide for Beryllium*. 1956.
18. American Industrial Hygiene Conference. Beryllium and its compounds. *Am Ind Hyg Assoc J*. 1964;25.
19. *Acceptable Concentrations of Beryllium and Beryllium Compounds (Z37.29-1970).* New York: American National Standards Institute; 1970.
20. US General Accounting Office. *Government Responses to Beryllium Uses and Risks (GAO/NSIAD/RCED/HEHS-00-92).* Washington, DC: US Government Printing Office; 2000.
21. Kanarek DJ, Wainer RA, Chamberlin RI, Weber AL, Kazemi H. Respiratory illness in a population exposed to beryllium. *Am Rev Respir Dis*. 1973;108:1295–1302.
22. Hardy HL. The Beryllium Case Registry. *Public Health Rep*. 1957;72:1066–1074.
23. Hardy HL. United States, Beryllium Case Registry (1952–1966). Review of its methods and utility. *J Occup Med*. 1967;9:271–276.
24. Hardy HL. Beryllium poisoning—lessons in control of man-made disease. *N Engl J Med*. 1965;273:1188–1199.
25. Peyton MF. Exposure data and epidemiology of the beryllium case registry. *AMA Arch Ind Health*. 1959;19:94–99.
26. Eisenbud M, Lisson J. Epidemiological aspects of beryllium-induced nonmalignant lung disease: a 30-year update. *J Occup Med*. 1983;25:196–202.
27. Hardy HL. Beryllium disease: a clinical perspective. *Environ Res*. 1980;21:1–9.
28. Office of Research and Development. *Health Hazard Assessment for Beryllium.* Washington, DC: US Environmental Protection Agency; 1987.
29. Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Beryllium (TP–92/04).* Washington, DC: US Department of Health and Human Services; 1993.
30. Stefaniak AB, Weaver VM, Cardorette M, et al. Summary of historical beryllium uses and airborne concentration levels at Low Alamos National Laboratory. *Appl Occup Environ Hyg*. 2003;18:708–715.
31. Johnson JS, Foote K, McClean M, Cogbill G. Beryllium exposure control program at the Cardiff Atomic Weapons Establishment in the United Kingdom. *Appl Occup Environ Hyg*. 2001;16:619–630.
32. Shima S. Beryllium poisoning and health care [Japanese]. *Sangyo Igaku*. 1980;3:14–22.
33. Shima S. A suggestion concerning medical prevention and control of chronic pulmonary berylliosis [Bates # D402192]. *Rodo Eisei*. 1974;8:18–24.
34. Shima S. Beryllium poisoning [Japanese]. *Techn Biol*. 1973;4:48–58.
35. Yoshida T, Shima S, Nagaoka K, et al. A study on the beryllium lymphocyte transformation test and the beryllium levels in working environment. *Ind Health*. 1997;35:374–379.
36. Ministry of Labour. *Working Environment Measurement System in Japan*. Tokyo: Japan Association for Working Environment Measurement; 1991.
37. Donaldson HM, Stringer WT. Beryllium sampling methods. *Am Ind Hyg Assoc J*. 1980;41:85–90.
38. Mroz MM, Balkissoon R, Newman LS. Beryllium. In: Bingham E, Cohrssen B, Powell CH, eds. *Patty's Toxicology, Volume 2, Toxicological Issues Related to Metals/Neurotoxicology and Radiation/Metals and Metal Compounds*. New York: John Wiley & Sons; 2000:177–219.
39. Cotes JE, Gilson JC, McKerrow CB, Oldham PD. A long-term follow-up of workers exposed to beryllium. *Br J Ind Med*. 1983;40:13–21.
40. Cullen MR, Kominsky JR, Rossman MD, et al. Chronic beryllium disease in a precious metal refinery. *Am Rev Respir Dis*. 1987;135:201–208.
41. Schuler CR, Kent MS, Deubner D, et al. Process-related risk of beryllium sensitization and disease in a copper-beryllium alloy facility. *Am J Ind Med*. 2005;47:195–205.
42. Sprince NL. Beryllium disease. In: Merchant JA, ed. *Occupational Respiratory Diseases (NIOSH Publication No. 86–102*). Washington, DC: US Department of Health and Human Services (NIOSH); 1986:385–399.
43. Kazemi H. Beryllium disease. In: Last JM, ed. *Maxcy-Roseneau Preventive Medicine and Public Health.* New York: Appleton-Century-Crofts; 1980:663–667.
44. Maier LA. Beryllium health effects in the era of the beryllium lymphocyte proliferation test. *Appl Occup Environ Hyg*. 2001;16:514–520.
45. Deodhar SD, Barna B, Van Ordstrand HS. A study of the immunologic aspects of chronic berylliosis. *Chest*. 1973;63:309–313.
46. Epstein PE, Dauber JH, Rossman MD, Daniele RP. Bronchoalveolar lavage in a patient with chronic berylliosis: Evidence for hypersensitivity pneumonitis. *Ann Intern Med*. 1982;97:213–216.
47. Williams WJ, Williams WR. Value of beryllium lymphocyte transformation tests in chronic beryllium disease and in potentially exposed workers. *Thorax*. 1983;38:41–44.
48. Rossman MD, Kern JA, Elias JA, et al. Proliferative response of bronchoalveolar lymphocytes to beryllium: a test for chronic beryllium disease. *Ann Intern Med*. 1988;108:687–693.
49. Deubner D, Kelsh M, Shum M, Maier L, Kent M, Lau E. Beryllium sensitization, chronic beryllium disease, and exposures at a beryllium mining and extraction facility. *Appl Occup Environ Hyg*. 2001;16:579–592.
50. Van Ganse WF, Oleffe J, Van Hove W, Groetenbriel C. Lymphocyte transformation in chronic berylliosis. *Lancet*. 1972;1:1023.
51. Van Ganse WF, Oleffe J, Van Hove W, Groetenbriel C. Lymphocyte transformation in chronic berylliosis. *Lancet*. 1972;1:1023.
52. Hanifin JM, Epstein WL, Cline MJ. *In vitro* studies of granulomatous hypersensitivity to beryllium. *J Invest Dermatol*. 1970;55:288.
53. Williams WR, Williams WJ. Development of beryllium lymphocyte transformation tests in chronic beryllium disease. *Int Arch Allergy Appl Immunol*. 1982;67:175–180.

54. Newman LS, Kreiss K, King TE Jr, Seay S, Campbell PA. Pathologic and immunologic alterations in early stages of beryllium disease. Re-examination of disease definition and natural history. *Am Rev Respir Dis*. 1989;139:1479–1486.
55. Kreiss K, Newman LS, Mroz MM, Campbell PA. Screening blood test identifies subclinical beryllium disease. *J Occup Med*. 1989;31:603–608.
56. Tepper LB, Hardy HL, Chamberlin RI. *Toxicity of Beryllium Compounds*. Amsterdam: Elsevier; 1961.
57. Kreiss K, Mroz MM, Zhen B, Martyny JW, Newman LS. Epidemiology of beryllium sensitization and disease in nuclear workers. *Am Rev Respir Dis*. 1993; 148:985–991.
58. Barna BP, Culver DA, Yen-Lieberman B, Dweik RA, Thomassen MJ. Clinical application of beryllium lymphocyte proliferation testing. *Clin Diagn Lab Immunol.* 2003;10:990–994.
59. Newman LS, Lloyd J, Daniloff E. The natural history of beryllium sensitization and chronic beryllium disease. *Environ Health Perspect*. 1996;104(suppl 5): 937–943.
60. Newman LS, Mroz MM, Balkissoon R, Maier LA. Beryllium sensitization progresses to chronic beryllium disease: a longitudinal study of disease risk. *Am J Respir Crit Care Med*. 2005;171:54–60.
61. Cullen MR. Screening for chronic beryllium disease: one hurdle down, two to go. *Am J Respir Crit Care Med*. 2005;171: 3–4.
62. Kreiss K, Mroz MM, Newman LS, Martyny J, Zhen B. Machining risk of beryllium disease and sensitization with median exposures below 2 $\mu g/m^3$. *Am J Ind Med*. 1996;30:16–25.
63. Henneberger PK, Cumro D, Deubner DD, Kent MS, McCawley M, Kreiss K. Beryllium sensitization and disease among long-term and short-term workers in a beryllium ceramics plant. *Int Arch Occup Environ Health*. 2001;74: 167–176.
64. Stange AW, Hilmas DE, Furman FJ. Possible health risks from low level exposure to beryllium. *Toxicology*. 1996; 111:213–224.
65. Barnard AE, Torma-Krajewski J, Viet SM. Retrospective beryllium exposure assessment at the Rocky Flats Technology Site. *Am Ind Hyg Assoc J*. 1996;57: 804–808.
66. Dinardi SR. *The Occupational Environment—Its Evaluation, Control and Management.* Fairfax, VA: American industrial Hygiene Association; 2003.
67. Eisenbud M, Wanta RC, Dustan C, Steadman LT, Harris WB, Wolf BS. Non-occupational berylliosis. *J Ind Hyg Toxicol*. 1949;31:282–294.
68. DeNardi JM, Van Ordstrand HS, Carmody MG. Chronic pulmonary granulomatosis. *Am J Med*. 1949;7:345–355.
69. Lieben J, Metzner F. Epidemiological findings associated with beryllium extraction. *Am Ind Hyg Assoc J*. 1959;20: 494–499.
70. Sussman VH, Lieben J, Cleland JG. An air pollution study of a community surrounding a beryllium plant. *Am Ind Hyg Assoc J*. 1959;20:504–508.