Beryllium: A Modern Industrial Hazard*

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Annu. Rev. Public Health 2007. 28:259–77

The *Annual Review of Public Health* is online at http://publhealth.annualreviews.org

This article's doi: 10.1146/annurev.publhealth.28.021406.144011

0163-7525/07/0421-0259$20.00

First published online as a Review in Advance on November 9, 2006

Key Words

berylliosis, sensitization, genetics, dermal exposure

Abstract

Beryllium exposure can cause a granulomatous lung disease in workers who develop a lymphocyte-mediated sensitization to the metal. Workers in diverse industries are at risk because beryllium's properties are critical to nuclear, aerospace, telecommunications, electronic, metal alloy, biomedical, and semiconductor industries. The occupational air concentration standard's failure to protect beryllium workers is driving many scientific and occupational health advances. These developments include study of bioavailability of different physicochemical forms of beryllium, medical surveillance to show effectiveness of skin protection in preventing sensitization in high-risk processes, gene-environment interaction, transgenic mice for use in experimental research, and risk-based management of industrial exposures in the absence of effective exposure-response information. Beryllium sensitization and disease prevention are paradigms for much broader public health action in both occupational and general population settings.

BACKGROUND/INTRODUCTION

Beryllium, a light-weight metallic element, was first recognized as a lung hazard in Europe in the 1930s, shortly after its first production in modern industry (18). In the United States, recognition of lung disease in association with beryllium exposure in two types of industries did not occur until the 1940s. The chronic lung disease was first described among workers exposed to beryllium-containing materials used in the manufacture of fluorescent lamps (21). In primary production of beryllium metal, which was used in nuclear weapons components, physicians recognized severe dermatitis, reversible pneumonitis, and chronic granulomatous lung disease (8, 69, 70). The public health community expressed its early confusion about the etiology of these diseases, publishing the erroneous view that the toxicity associated with beryllium salts was due to the fluoride component of those salts, which were found in the preparation of the metal (25).

PHYSICOCHEMICAL DETERMINANTS OF DISEASE

In hindsight, we now recognize that physicochemical properties of beryllium compounds may account for the differing clinical presentations in different industries. In primary production of beryllium metal, soluble salts were present and caused rashes in approximately one fourth of exposed workers and reversible acute pneumonitis in a smaller portion of the workforce. After heavy inhalation exposures, radiographic abnormalities evolved at approximately three weeks; resolution of symptoms and radiologic abnormalities away from exposure occurred only after months, but symptoms recurred immediately upon reexposure (8). Some acute pneumonitis cases progressed at long interval to chronic irreversible granulomatous lung disease (20), often after those workers were transferred to industrial processes involving production of copper-beryllium alloy, which was not considered hazardous at the time (56). Beryllium oxide, a relatively insoluble compound, was used in the ceramics industry. Another relatively insoluble beryllium-containing compound, in the form of phosphor, was present in the fluorescent light industry until 1949 (13). Inhalation of relatively insoluble (and therefore biologically persistent) dusts of beryllium compounds caused irreversible and progressive lung disease in a subset of workers. In contrast, soluble beryllium salts caused skin and lung disease, which disappeared when exposure ceased, probably because the salts were excreted. Although textbooks still describe historical "acute beryllium disease" as a toxic pneumonitis resulting from high exposures, the clinical course is more consistent with a hypersensitivity condition.

BERYLLIUM SENSITIZATION AND DISEASE

The granulomatous nature of chronic beryllium disease is now known to be caused by cell-mediated sensitization to beryllium. Sensitization can be measured in vitro with a beryllium-specific lymphocyte proliferation test using either white blood cells or bronchoalveolar lavage cells. Since 1987, this biomarker of sensitization has enabled medical surveillance of beryllium-exposed workforces (31). Beryllium lymphocyte proliferation tests have been used to screen workers to detect sensitization (**Table 1**), to characterize epidemiologically workplace risks for beryllium sensitization, and to evaluate the effectiveness of interventions intended to prevent sensitization.

Today, most chronic beryllium disease is diagnosed subsequent to identification of sensitization, using outpatient bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. Thus, most disease diagnosed today is subclinical. Sensitized workers without lymphocytic alveolitis and granulomatous lung disease on initial clinical evaluation are at high risk for development of chronic beryllium disease. One recent study

followed 55 sensitized workers who did not have chronic beryllium disease at the time that sensitization was detected; one third developed chronic beryllium disease within an average follow-up period of less than four years (43). Those that were followed after development of chronic beryllium disease had declines in pulmonary function during an average follow-up time of less than five years. However, some sensitized workers followed as long as 12 years had not developed chronic beryllium disease.

Beryllium lymphocyte proliferation test results are not always consistent or stable; investigators have demonstrated differences between laboratories testing split samples or testing samples over time (9, 30, 55). Whether these differences are a biologic or laboratory phenomenon is not clear in the case of individuals, and the vagaries of beryllium lymphocyte proliferation testing are challenging in the context of interpretation of screening test results. In addition, the complex immunological basis for the test is incompletely understood. Despite limitations in test consistency and repeatability, beryllium lymphocyte proliferation testing has been an invaluable tool in the identification of workplace risks in population studies and of intervention effectiveness (2, 10, 22, 28–32, 44, 50, 52, 55, 60, 62, 63, 73).

SCREENING AND MEDICAL SURVEILLANCE

Debate about the use of the beryllium lymphocyte proliferation test for worker screening continues. Current beryllium-exposed workers may benefit from screening, which can be defined as "the search for previously unrecognized diseases or physiological conditions that are caused or influenced by work-associated factors" (34), in that they can choose to limit further beryllium exposure if found to be sensitized. However, it is not certain that curtailing additional lung dose improves the long-term prognosis in sensitized workers because they may already have a sufficient lung burden of the metal to sustain development of chronic beryllium disease. Workers exposed to persistent (relatively insoluble) beryllium antigen in industries with beryllium oxide, beryllium alloy, and/or metal are at lifelong risk of chronic beryllium disease (13, 27). Clinical cases of beryllium disease sometimes present decades after leaving beryllium exposure (32). Among former beryllium workers with symptoms of interstitial lung disease, beryllium lymphocyte proliferation testing is a critical tool for differential diagnosis. Currently, treatment of beryllium disease with corticosteroids or other immunosuppressive therapy is deferred until objective abnormalities develop because of the adverse health effects of treatment (37). Hence, early diagnosis of asymptomatic disease among former beryllium workers may be of limited immediate utility with respect to treatment. Additionally, psychological and social harm may result from diagnosis of a condition before treatment is indicated, for example, stigmatization and discrimination in insurability and employment. However, the Energy Employees Occupational Illness Compensation Program Act of 2001 (7) provides for medical care and remuneration for those diagnosed with chronic beryllium disease.

In contrast with the debate surrounding the use of the test for screening, its utility in medical surveillance for setting priorities for preventive strategies in worker populations is uncontested (9, 61). Surveillance has been defined as "the continued watchfulness over the distribution and trends of incidence through the systematic collection, consolidation and evaluation of morbidity and mortality reports and other relevant data" (33) for the purposes of prevention of disease or injury. Worker screening leads to secondary prevention, at best, unless it is part of a population-based surveillance program in which work-related risks are identified and preventive interventions are undertaken and evaluated for efficacy in preventing new disease. From a public health perspective, emphasis must be on primary prevention.

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) Beryllia 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) Beryllia 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.

PRIMARY PREVENTION

Primary prevention of chronic beryllium disease through control of beryllium exposure in air has largely failed. In 1949, the Atomic Energy Commission implemented a beryllium standard of 2 $\mu g/m^3$ as an 8-hour time-weighted average, which was later adopted by the Occupational Safety and Health Administration (OSHA) as a legally permissible exposure limit (45). This standard was constructed on the basis of beryllium's atomic weight relative to that of heavier "toxic" metals, such as lead, which had an occupational standard at the time of 100 $\mu g/m^3$ (11). As such, establishment of the beryllium standard had no epidemiological basis (12). For decades, this standard was judged to be protective for acute beryllium pneumonitis, which was no longer observed in the primary manufacture of beryllium, and for chronic beryllium disease. Sporadic clinical cases were attributed to upset conditions (e.g., accidental spills), which were invariably identified in clinical work histories of ill workers.

Beryllium lymphocyte proliferation testing destroyed complacency with this occupational standard because cases were now detected in workforces thought to have reasonable compliance with the 2 $\mu g/m^3$ standard (22, 28) (**Table 1**). When historical exposure data were available, no consistent associations were apparent between cumulative or average exposure and beryllium sensitization or disease.

PROCESS-RELATED RISK

Cross-sectional studies of beryllium-exposed workforces demonstrated associations between particular industrial processes and increased prevalence of beryllium sensitization and/or chronic beryllium disease (**Table 2**) (22, 28–30, 32, 55, 62). Despite concerns that hypersensitivity could make exposure-response relations difficult to ascertain, process-related risks indicated that heretofore unmeasured exposure characteristics increased the likelihood of beryllium sensitization and disease. These unmeasured characteristics were likely physicochemical properties of the exposure materials that determined the degree of beryllium bioavailability and the resultant immune response. Early studies documented that machining of metal and ceramic conferred excess risk (28, 29, 31), as did certain operations in primary metal production (30), research and development work (32), pressing of ceramic parts (32), and analytical laboratory work (30). Thus, subsequent preventive measures logically targeted such high-risk areas, regardless of whether exposures were in compliance with the mass-based regulatory standard.

Following implementation of such engineering controls, the resultant reduction in mass-based airborne beryllium exposures did not prevent sensitization. In the best-studied facility, machining exposures were curtailed by enclosing and exhausting all machining operations; sensitization was reduced for machinists hired subsequently, but overall prevalence at the facility increased (22). Very low overall airborne beryllium levels at a copper-beryllium alloy finishing facility were associated with levels of sensitization similar to levels at facilities with much higher airborne concentrations (55). These experiences challenged the conventional industrial hygiene approach, which emphasized engineering controls to reduce hazardous exposures in the workplace. Clearly, a more rigorous and perhaps novel approach was necessary to reduce the potential for exposure and, thus, to prevent occupational disease. This comprehensive approach included concurrent attention to limiting the number of workers in higher-hazard jobs; particle migration control through better housekeeping, attention to surface contamination, air showers, and sticky floor mats; and the addition of dermal protection to respiratory protection. Intensive medical surveillance of new employees for beryllium sensitization allowed documentation of

the early success of this more comprehensive approach in comparison with a standard approach that relied heavily on engineering controls to lower air concentrations (2).

DERMAL EXPOSURE

Workers in primary beryllium production in the 1940s developed dermatitis when exposed to soluble salts and, in fact, were dismissed from employment with the concern that they could be more susceptible to occupational lung disease (70). Skin disease among workers exposed to poorly soluble beryllium-containing particles was rare, apart from wound contamination, and skin protection from poorly soluble particulate beryllium was not considered a component of the exposure reduction strategy until control of inhalation exposures alone had failed to prevent beryllium sensitization among new workers. Consideration of skin protection triggered both reexamination of historical medical literature and new scientific investigation.

In the 1950s, Curtis (3) had demonstrated skin sensitization to beryllium with patch testing using soluble salts in beryllium-naïve subjects, who subsequently developed granulomatous skin lesions and a typical delayed-type contact dermatitis with repeat challenge. More than 50 years later, Tinkle and colleagues (68) showed that synthetic beads of up to 1 μm in diameter could move from the surface of human skin into the dermis where immunologically active cells are located. They also reported that relatively insoluble beryllium oxide particles placed onto the surface of the skin of mice resulted in an immune reaction when the mice were subsequently challenged by dermal application of a beryllium salt. Indeed, beryllium sensitization was demonstrated with a beryllium lymphocyte proliferation test using pooled cells from draining auricular lymph nodes. Such sensitization by the dermal route is consistent with development of abnormal blood beryllium lymphocyte proliferation tests prior to development of granulomatous lung disease. Presumably, lung disease in a sensitized person would require a lung burden of beryllium against which lung lymphocytes would mount a granulomatous response (6). Sensitization without a lung burden may not lead to chronic beryllium disease.

Control of dermal exposure to beryllium, as a possible means of preventing sensitization, is not easy. In addition to proper glove use, comprehensive dermal protection requires impeccable housekeeping; beryllium particulate migration control at process, work area, and worksite levels; and constant efforts to keep beryllium off clothing, gaps between clothing and gloves, and other areas of exposed skin. Challenges for avoiding skin contact with a sensitizing substance differ quantitatively from a toxic substance for which skin barrier properties may be adequate. Early evaluation of the effectiveness of protective gloves documented beryllium contamination of the hands under occlusive gloves traced to contact with beryllium-contaminated shoes and respirators before donning protective gloves (2). Despite evolution of skin-protection measures over a two-year period, efficacy of these comprehensive measures of particulate migration control and skin protection, in addition to the engineering and respiratory protection controls, has shown early evidence of being effective. Employees hired after the comprehensive program including skin protection had sensitization incidence of 0.7 cases per 1000 person-months' employment in the first 5 years of the program compared with 5.6 cases per 1000 person-months previously (2). Longer-term study of this cohort, including workers who have left employment, is necessary to see whether sensitization has been merely delayed rather than prevented. The plausible impact of lowering lung burden by engineering controls and respiratory protection on incidence of beryllium disease among the sensitized likewise needs long-term follow-up.

Table 2 Process-related risk of beryllium sensitization and disease by industry and study[a]

Study and industry	Job or process	BeS (%)	CBD (%)
Kreiss et al. 1993[b] (29)	Machinists	4.7%	n/a
Nuclear weapons facility	Metallurgical operator	4.6%	
Kreiss et al. 1993 (32)	Dry pressing	15.8%	15.8%
Beryllia ceramics	Process development/engineering	13.6%	13.6%
	Ventilation maintenance	11.1%	11.1%
Kreiss et al. 1996[c] (28)	Lapping	20.0%	n/a
Beryllia ceramics	Machining	14.3%	
Kreiss et al. 1997 (30)	Ceramics production	11.6%	9.0%
Be metal, alloy, and oxide production	Be metal pebble plant[e]	13.4%	5.2%
	Analytic laboratory[f]	20.0%	4.0%
Henneberger et al. 2001[c,d] (22)	Lapping	21.1%	n/a
Beryllia ceramics	Machining	17.5%	
	Forming	15.6%	
	Firing	14.9%	
Stange et al. 2001[b] (62)	Beryllium machinists	11.9%	8.5%
Nuclear weapons facility	Health physics	11.9%	4.8%
	Construction trade	10.0%	2.6%
Schuler et al. 2005 (55)	Point and chamfer	21.4%	21.4%
Copper-beryllium alloy finishing	Wire pickling and annealing	12.5%	10.3%
	Wire drawing	13.6%	9.5%

[a]Results presented are significant at the $p < 0.10$ level.
[b]Same facility.
[c]Same facility.
[d]Results are presented for long-term workers (employed six years or more; first surveyed in 1992 but none sensitized at that time).
[e]All ceramics workers removed from this analysis.
[f]All ceramics and pebble plant workers removed from this analysis.

RISK-BASED MANAGEMENT

Prevention of beryllium-related conditions can serve as a paradigm for occupational health-preventive strategies when standards are not protective, nonexistent, or not enforced. Such is the case for many industrial situations, owing to the introduction of new chemicals and the discovery of toxicity among regulated chemicals, and in the many countries with inadequate regulatory infrastructure and enforcement. With beryllium, 15 years of epidemiologic studies have shown that the existing 2 $\mu g/m^3$ standard is not protective. Attempts to define a safe air concentration of beryllium for all workers are not likely to be successful. One reason for pessimism lies in the varying risks posed by physicochemical characteristics of different beryllium compounds and process aerosols. In one facility with diverse processes, the dissociation between mass inhalation exposure measurements and risk of sensitization was particularly evident (30). Parts of the facility with average exposures above the regulatory standard had lower risk, whereas certain operations in primary metal production had extremely high risk of sensitization at much lower exposure levels. Attempts to characterize beryllium-containing particles in terms of chemistry, size, surface area, and solubility in body fluid compartments and cells may result in biologically relevant hazard information (5, 64–67). In the meantime, environmental measurements of beryllium air concentrations are of limited use in counseling

workers about risk, motivating use of respiratory protection, or stimulating preventive priorities.

In contrast, implementation of engineering controls, particle migration control, and respiratory and dermal protection can be prioritized on the basis of higher-risk processes. Medical surveillance, if feasible, can evaluate the effectiveness of interventions in particular work sites after resources are expended for primary prevention. The persistence of risk from historical exposures (22, 30) requires beryllium lymphocyte proliferation testing of previously unexposed (new) employees to evaluate interventions.

A new comprehensive preventive paradigm is based on management of process-related risk of adverse health outcomes using tools to address simultaneously exposure containment, respiratory protection, and skin protection. This approach contrasts with compliance-based management of occupational disease risk, which more commonly adopts a hierarchy of controls with the assumption that a permissible exposure limit is protective. No guidelines are available with which to propose regulating allowable skin exposure in the beryllium or other industry. One solution is to consider substituting beryllium with a lower-risk material. If substitution is not possible, then successful management of process-related risk may require an increase in corporate commitment to safety culture, empowerment of employees to improve their work environments through housekeeping and particle migration control, and unrelenting education about exposure pathways and risks.

Currently, the only guidance for prevention efforts comes from epidemiologic findings of process-related risks and of early efficacy of comprehensive exposure reduction with attention to skin protection as well as respiratory protection. Quantitative guidelines are unavailable for either exposure route. The burgeoning attention to physicochemical characteristics of process aerosols associated with increased risk is likely the key to predicting relative risk of processes in unstudied facilities and evolving production technologies.

PHYSICOCHEMICAL DETERMINANTS OF RISK

Physicochemical characteristics of low- and high-fired beryllium oxides, such as particle size and surface area, have been available for more than 50 years (19); however, physicochemical characterization of other high-risk process-generated aerosols is incomplete. To date, the high-risk processes in primary beryllium metal production have shown particle number concentrations in the submicron size range that are orders of magnitude higher than those found in lower-risk processes in the same facility (39). Distinguishing characteristics of machining aerosols in metal machining are limited (24). In a beryllia ceramics plant with excess sensitization risk among machinists, machinists had the highest beryllium mass exposure concentrations when compared with other job titles (28); the apparent exposure-response relationship was likely due to uniform particle size distribution across all processes (M. McCawley, unpublished observations). Among analytic laboratory workers, exposures to soluble forms of beryllium may be more likely than for other workers in the facility, and this characteristic is a reasonable hypothesis for their excess risk of sensitization (and not for chronic beryllium disease) (30). In a copper-beryllium alloy facility, higher-risk processes within rod and wire production had the highest average exposures to beryllium and the most exceedances of a target action level of 0.2 $\mu g/m^3$ (55). Additionally, workers in these processes had the highest indices of skin loading with beryllium compared with workers involved in lower-risk processes (4). Information is rapidly evolving regarding the physicochemical characterization of process-generated aerosols (66, 67) and skin contamination indices across processes (4), in conjunction with health risks of sensitization and disease.

GENETICS

Exposure to beryllium is necessary for development of chronic beryllium disease; however, differential susceptibility to chronic beryllium disease clearly has a genetic component. The genetic basis of immunologic reactivity to beryllium involves human leukocyte antigens (HLA); the beryllium-induced proliferation of T lymphocytes from lungs of chronic beryllium disease patients was blocked by antibodies directed against the DP subgroup of HLA (16, 54). Many studies have shown that HLA-DP alleles having a glutamic acid in the sixty-ninth position of the B1 chain of this molecule confer higher risk of chronic beryllium disease and sensitization (36, 38, 48, 49, 51, 53, 71, 72). Such *HLA-DPB1*^{Glu69} alleles are present in approximately one third of the unaffected populations studied (48, 49, 72, 74). The *HLA-DPB1*^{Glu69} marker has poor positive predictive value because of its high prevalence in the population and the relatively low prevalence of chronic beryllium disease, limiting its use as a genetic screening tool. In addition, ~10%–25% of those with chronic beryllium disease do not have the marker.

Nonetheless, more specific genetic tests may soon be available with much greater positive predictive value. In one study of three beryllium facilities, 4% of the participants had two copies of the *HLA-DPB1*^{Glu69} marker (homozygous) and 29% had one copy (heterozygous); the risk of chronic beryllium disease to the former was three times greater than the risk to the latter (38). Among the 119 known *HLA-DPB1* alleles, the 42 alleles with glutamic acid in the sixty-ninth position can be divided into subsets that fall into a risk hierarchy. Computational chemistry modeling of different alleles indicates that the variable portions of the molecule affect the surface electronegativity and shape of the antigen binding groove (59). When classified by electronegativity, subgroups with the greatest electronegativity have the greatest association with chronic beryllium disease status (75) (**Figure 1**). In addition, calculated binding energy for beryllium, in comparison with other divalent cations, demonstrates an association with beryllium disease status (58). This new multidisciplinary approach of computational chemistry, genetics, and epidemiology holds promise of identifying a genetic test for high-risk *HLA-DPB1*^{Glu69} alleles present in a small proportion of workers with very high risk of chronic beryllium disease. Insofar as chronic beryllium disease risk differs from sensitization risk among particular allele subgroups, such a genetic test could have prognostic import for the sensitized. Preliminary data suggest that such a subgroup of alleles exists.

ETHICS OF GENETIC TESTING

Advances in genetic understanding of risk raise ethical concerns regarding which parties have access to the genetic characterization of individuals. Employers with access to genetic characteristics of their current employees would be hard-pressed to avoid the appearance of workplace discrimination. Employers with access to genetic characteristics of potential employees could limit their liability for some chronic beryllium disease cases without ensuring safe conditions of work by denying employment to the more susceptible. Although some states have statutes prohibiting genetic discrimination, no federal regulations exist except to prohibit discrimination among federal workers (15). Similarly, insurability for a "preexisting" genetic susceptibility is a matter of ethical concern, even though beryllium exposure is necessary for development of chronic beryllium disease. At the present time, no research-based information is available to workers currently in the beryllium industry regarding whether their risks of sensitization or disease are lessened by cessation of exposure, with or without increased genetic susceptibility. The group most likely to benefit from genetic testing with high positive predictive value is employees new to the beryllium industry, prior to any exposure. If

such testing were available confidentially, for example from a public health agency, job seekers could weigh their risks of sensitization and disease against their risk tolerance and other opportunities. However, guarantee of confidentiality of personal information for nonresearch purposes is an area of public health law that has not been developed. Numerous precedents exist for limiting benefits to workers who are presumed to have assumed risk (17, 26).

The knowledge posed by the available cross-sectional studies of genetic characteristics of worker populations in relation to sensitization and disease is limited. Information about gene-environment interaction is not yet available because of the small size of populations studied to date (48) and the lack of good exposure information on most populations. Similarly, longitudinal risk of sensitization and disease is likely much greater than cross-sectional risk. The one study currently available suggests that a small beryllia ceramics cohort followed for 11 years had 2.7-fold higher risk of becoming sensitized and 2.5-fold higher risk of developing chronic beryllium disease than was evident in the initial cross-sectional study (27). No work exists yet to examine the risks of genetic subgroups of these cohorts, although these investigations are underway. Such information is critical for genetic counseling, should more specific genetic tests be developed. In parallel, when such tests become available, confidential preemployment genetic testing of prospective employees should be evaluated in a research setting to determine whether such information is of value to job candidates in primary prevention of chronic beryllium disease.

MURINE MODELS

Transgenic mice, designed to contain three different human *HLA-DPB1* alleles associated with different levels of epidemiologic risk for beryllium disease, are being evaluated (A. Weston, unpublished observations). The alleles are *HLA-DPB1*0401*, which is not associated with chronic beryllium disease (and lacks glutamic acid in position 69); *HLA-DPB1*0201*, which conveys moderate risk of chronic beryllium disease (relative risk of about 2); and *HLA-DPB1*1701*, which conveys high risk (relative risk of about 10) (the latter two alleles having glutamic acid in position 69). With these murine models, experimental studies can be conducted of risk in relation to beryllium physicochemical characteristics and route of exposure in the context of human genetic variants. These models may also be useful in exploring pharmacologic interceptors of beryllium sensitization and new therapeutic agents for chronic beryllium disease.

EXTENT OF PUBLIC HEALTH PROBLEM

Workers at risk for developing sensitization and chronic beryllium disease include those engaged in all operations that produce or use beryllium and its compounds, apart from exposure associated with mining and cutting gemstones. Beryllium is a light-weight metal with many applications. It adds strength, flexibility, and electrical conductivity to other metals with which it is alloyed, provides neutron-moderating properties for nuclear weapons and nuclear energy, allows transparency to x-rays in medical diagnostic devices, and has thermal conductive properties beneficial in the specialty ceramics and computer chip manufacturing industries. As a critical component of modern electrical and electronics technology, especially in the telecommunications industry, its use is steadily becoming more widespread and diverse. Beryllium production workers have been thought to have the highest prevalence of disease. However, prevalence of disease in workers downstream of primary production has not been studied systematically. In a recent study, persons initially diagnosed with sarcoidosis in Europe and Israel, who worked in diverse industries, have since been diagnosed with chronic beryllium disease or sensitization (40). Exposures

Table 3 Industries using beryllium in products

Industry	Products
Aerospace	Altimeters, braking systems, bushings and bearings for landing gear, electronic and electrical connectors, engines, gyroscopes, mirrors (e.g., space telescopes), precision tools, rockets, satellites, and structural components
Automotive	Air-bag triggers, antilock brake system terminals, electronic and electrical connectors, steering wheel connecting springs, and valve seats for drag racing engines
Biomedical	Dental crowns, bridges, partials, and other prostheses, medical laser and scanning electron microscope components, and x-ray tube windows
Defense	Heat shields, mast-mounted sights, missile guidance systems, nuclear reactor components and nuclear triggers, submarine hatch springs, and tank mirrors
Energy and electrical	Heat exchanger tubes, microelectronics, microwave devices, nuclear reactor components, oil field drilling and exploring devices, and relays and switches
Fire prevention	Nonsparking tools and sprinkler system springs
Instruments, equipment, and objects	Bellows, camera shutters, clock and watch gears and springs, commercial speaker domes, computer disk drives, musical instrument valve springs, pen clips, and commercial phonograph styluses
Manufacturing	Injection molds for plastics
Sporting goods and jewelry items	Golf clubs, fishing rods, naturally occurring beryl and chrysoberyl gemstones such as aquamarine, emerald, and alexandrite, and manmade gemstones such as emeralds with distinctive colors
Scrap recovery and recycling	Various beryllium-containing products
Telecommunications	Cellular telephone components, electromagnetic shields, electronic and electrical connectors, personal computer components, rotary telephone springs and connectors, and undersea repeater housings

to beryllium can occur in the aerospace, specialty ceramics, dental technology, and other industries listed in **Table 3**.

On the basis of compliance sampling data from OSHA, measurable beryllium exposures occur in diverse industries with an estimated U.S. employment of 134,000 persons (23). This figure is likely an underestimate because OSHA has not conducted sampling for beryllium in military and nuclear weapons cycle workplaces nor in many workplaces where beryllium is a minor or unsuspected component, as in aluminum smelting, scrap recovery, and electronics recycling. The number of U.S. workers ever exposed to beryllium is thus likely to far exceed the estimate above, including approximately 250,000 construction workers at nuclear weapons reclamation sites alone. Workers with former beryllium exposure have been identified as sensitized and diagnosed with chronic beryllium disease years after beryllium exposures have ceased (27, 32, 60, 62, 73).

In addition to workers known to have been exposed to beryllium, chronic beryllium disease can occur among those judged to have had trivial, unrecognized, or brief exposure to beryllium. Examples include secretaries (13, 28, 29), security guards (29), building trade workers (73), end-product inspectors (29), and workers hired years after beryllium operation ceased in particular facilities (13, 32). In the 1940s, cases of beryllium disease were recognized in residents living near beryllium refineries and fluorescent light factories (13, 14). Family members of beryllium workers have developed beryllium disease, perhaps by having contact with contaminated clothing (13, 14, 35, 42). Persons with these types of bystander or unrecognized beryllium exposures

may have increased genetic susceptibility accounting for their development of chronic beryllium disease and may be missed in estimates of the extent of at-risk populations based on compliance sampling.

BERYLLIUM AS PARADIGM

Public health approaches to beryllium hazards can be a model for prevention relevant to large portions of the working population. In addition, study of beryllium-related health effects can be a pertinent paradigm for several population health problems, beyond those encountered in occupational settings.

With respect to conceptual frameworks for occupational health, the regulatory standard for beryllium air concentration does not prevent beryllium sensitization or chronic beryllium disease. Thus, beryllium workers are representative of the many workers throughout industry who are not protected by current recommended exposure limits. In addition, of the 60,000 chemicals accounting for most commercial chemical use, only 881 have either a permissible exposure limit or a recommended exposure limit. As a consequence, many hazardous exposures to workers are unregulated. In instances of absent or nonprotective exposure standards, risk-based approaches to managing materials and processes are useful in preventing occupational diseases; one form of risk-based management is known as control banding (41, 46). Identifying and controlling high-risk processes in the beryllium industry, without regard to measurement of air concentrations, have been necessary to protect beryllium worker health. Similar approaches may be particularly attractive to small businesses with 100 or fewer employees, which employ 85% of all U.S. workers. Small businesses rarely employ industrial hygiene measurement consultation but can be guided to prevent disease by implementing appropriate risk-based controls.

Measuring beryllium mass concentrations in air does not predict risk of sensitization or chronic beryllium disease. Thus, beryllium may serve as a paradigm for refining risk estimates on the basis of bioavailability of different forms of beryllium. The determinants of bioavailability are likely physicochemical characteristics such as particle size, surface area, and solubility in skin, interstitial lung, and phagocytic fluids. Study of these characteristics in relation to health risk by process in the beryllium industry will likely motivate similar work for the cobalt, hard metal, and nanotechnology industries, in which discrepancies exist between mass concentrations and likely health risks.

Sensitizers have confounded those interested in exposure-response relationships as a basis of risk assessment. Evidence that sensitization is exposure related exists for many substances, for example isocyanates and enzymes (1). Once sensitized, workers can react to much lower levels of exposure, sometimes below limits of detection. This phenomenon has resulted in occupational exposure standards for sensitizers being nonprotective of the sensitized subpopulation of workers. Beryllium studies have contributed to the study of sensitizers in at least two paradigmatic ways. First, the ability to measure immunologic response to a known antigen with the beryllium lymphocyte proliferation test has allowed study of workforces for sensitization risk by process and exposure characteristics. Such an immunologic marker of response does not exist for most sensitizers, in which complex chemical (e.g., isocyanate polymers) and microbial characteristics preclude identification of a single antigen. Second, the likelihood of skin sensitization to beryllium is a paradigm for prevention of sensitizer exposure that is surely applicable to many other sensitizers. For example, isocyanate stains on clothes and skin have been shown to be a predictor of work-related respiratory symptoms in a cohort of workers in a new wafer board plant using isocyanates (47). The challenge of preventing skin exposures to sensitizing beryllium-containing particles is being pioneered in the primary beryllium production industry. This work may well be important to controlling

aeroallergen skin exposure, which contributes to eczema and asthma in infants and children.

Another example of beryllium studies changing conventional workplace occupational safety and health practice concerns the differentiation of screening and surveillance. Screening is mandated by regulation for several occupational exposures, such as cotton dust, asbestos, and lead (57). However, screening to identify occupational disease conditions is useful only for secondary prevention of those workers identified in screening programs. 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. Within the beryllium industry, collecting information on a population basis, which allows linking of the characteristics of persons identified as sensitized to work processes or types of exposure, has resulted in identifying priorities for primary prevention. In addition, surveillance at regular intervals has shown that well-intended control of air exposures to beryllium, both by engineering controls and by respiratory protection, failed to prevent beryllium sensitization. Similarly, surveillance using screening data has suggested that skin protection from exposure has lowered sensitization rates early in employment. Many industry screening efforts could have primary prevention impacts if they were conducted with the intent of surveillance, using population-based collection of potential risk factor information.

Beryllium studies are paradigmatic for studying the interaction of genetic susceptibility with environmental exposure. Genetic studies have advanced understanding of the molecular mechanisms of immunologic recognition of beryllium, particularly in the recent modeling of the beryllium-binding antigen groove of the HLA alleles conferring different risks of beryllium disease. Researchers' ability to identify biologic response to beryllium lays the basis for studies that will show whether common genetic subgroups in the general population feasibly can be protected from adverse effects by lowering exposure standards and implementing comprehensive protection from skin exposure. This evolving science will advance thinking about and practice of genetic testing of occupational populations in a concrete way. Inasmuch as HLA molecules are central to nonoccupational immunogenic diseases (e.g., sarcoidosis and musculoskeletal and autoimmune diseases), the examples of chronic beryllium disease and murine studies could be invaluable.

In summary, recent advances in understanding beryllium and its adverse effects of sensitization and chronic beryllium disease have benefits in the scientific and public health communities far greater than would be expected given the size of the exposed worker population. These benefits include paradigms for biomarkers of effect (sensitization), which allow study of risk factors and effectiveness of interventions to lower risk; sensitizing exposures causing asthma, hypersensitivity pneumonitis, and contact dermatitis; novel methods of exposure assessment pertinent to bioavailability, dose calculation, and biologic risk; innovative approaches to prevention in the workplace using concurrent methods to lower risk; medical surveillance for primary prevention purposes using screening data, which is usually used for secondary prevention; gene-environment interaction; and ethics of genetic testing. The dissemination of the advances in the beryllium industry and the science pertinent to it can have wide impact because of the many industries in which beryllium materials are present. Insofar as risk-based control of exposures is successful in the beryllium industry, this approach becomes a model for prevention in

the many other industries in which occupational exposure standards do not exist, are not protective, or are not enforced. Successful intervention to prevent sensitization probably requires corporate culture change with long-term effects on worker empowerment, training, and lowering of accident rates as well. Finally, the scientific advances pertaining to beryllium may lead the way in other areas of molecular immunology and therapeutics for diseases affecting general populations.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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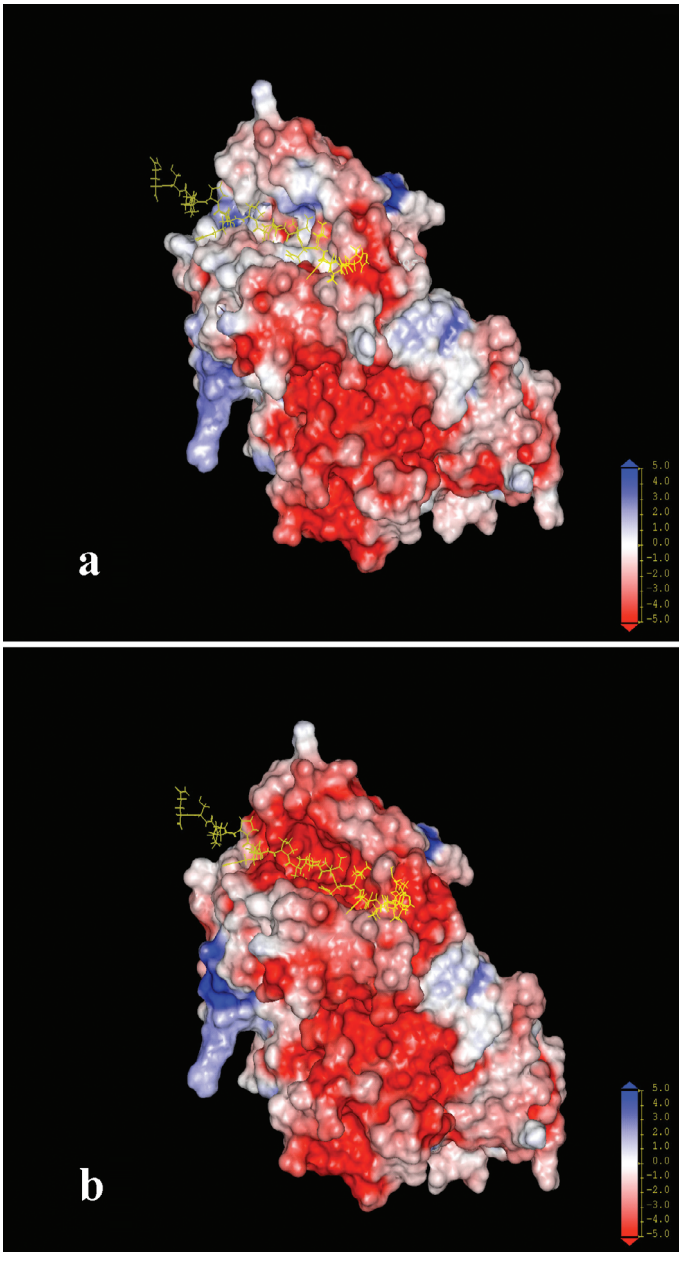

Figure 1

Computational models of HLA-DP protein structures showing relative surface charge distributions (*blue*: positive charge; *red*: negative charge; *white*: neutral). The yellow stick figure of a myelin molecule indicates the position of the HLA binding groove. (a) a B-chain molecule coded for by *HLA-DPB1*0401*, with lysine at B69; (b) a B-chain molecule coded for by *HLA-DPB1*1701*, with glutamic acid at B69. Additionally, *HLA-DPB1*0401* codes for the neutrally charged alanine at B55 and B56 as well as neutrally charged glycine residues at B84 and B85, whereas *HLA-DPB1*1701* codes for the negatively charged glutamic acid at B55 and B85 and the negatively charged aspartic acid at B56 and B84; all these positions are present in the binding groove.

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