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SHORT COMMUNICATION

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Beryllium exposure: dermal and immunological considerations

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Abstract *Objective*: People exposed to beryllium compounds are at increased risk of developing beryllium sensitization and chronic beryllium disease (CBD). The purpose of this short communication is to present information regarding the potential importance of skin exposure to beryllium, an exposure and alternate immune response pathway to the respiratory tract, which has been largely overlooked in epidemiologic and exposure assessment studies. *Methods*: We reviewed the published literature, including epidemiologic, immunologic, genetic, and laboratory-based studies of in vivo and in vitro models, to assess the state of knowledge concerning skin exposure to beryllium. *Results*: Reduction in inhalation exposure to beryllium has not resulted in a concomitant reduction in the occurrence of beryllium sensitization or CBD, suggesting that continued prevalence may be due, in part, to unchecked skin exposure to beryllium-containing particles. *Conclusions*: Recent developments in our understanding of the multiple exposure pathways that may lead to beryllium sensitization and CBD suggest that a prudent approach to worker protection is to assess and minimize both skin and inhalation exposures to beryllium.

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Beryllium as a strategic resource

Beryllium is a light, hard, silver gray metal with a unique combination of physical, mechanical, and nuclear properties not found in any other metal (Stonehouse and Zenczak 1991). Because of these physicochemical properties, the metal and its oxide and alloys are widely used in a large number of technological applications (Kolanz 2001; Weston et al. 2005, in press). The US National Institute for Occupational Safety and Health has estimated as many as 134,000 current workers in government and private industries are potentially exposed to beryllium in the United States (Henneberger et al. 2004).

Beryllium metal is stiffer than steel and is a neutron moderator, hence its application as a nuclear trigger. It is also used in inertial guidance systems, spacecraft, satellites, and fire control and navigation systems. Beryllium oxide has a high thermal conductivity and heat capacity, unusual resistance to thermal shock, and very low electrical conductivity, making it useful as substrate material for high-speed integrated circuits or as electrical insulators in jet aircraft engine igniters. The metal is most commonly alloyed with copper, producing a ductile material that is non-sparking, resistant to fatigue, and highly electrically conductive. Copper-beryllium alloy products are used in many applications including electronics and electrical equipment, springs and non-sparking tools, and wireless communications.

Beryllium sensitization and CBD

A fraction of people exposed to beryllium compounds become sensitized, meaning that their immune systems respond to beryllium exposures. The prevalence of beryllium sensitization in some exposed worker

populations has been reported to range between 0.8 and 12% (Kreiss et al. 1989, 1993a, 1996, 1997; Henneberger et al. 2001; Sackett et al. 2004; Stange et al. 2004; Schuler et al. 2005). Sensitization is thought to precede the development of chronic beryllium disease (CBD) (Newman et al. 2005), a slowly progressive respiratory disease, characterized by the formation of inflammatory injuries known as granulomas (i.e., compactly grouped cells that replace normally functioning tissue). The prevalence of CBD in exposed worker populations is lower than sensitization prevalence, and has been reported to range between 0.4 and 8% (Kreiss et al. 1989, 1993a, b, 1996, 1997; Henneberger et al. 2001; Sackett et al. 2004; Stange et al. 2004; Schuler et al. 2005). Not all individuals who become sensitized may progress to disease (Newman et al. 2005), suggesting that sensitization is a necessary but insufficient condition for disease development.

Recognition of sensitization and disease

Although beryllium sensitization is asymptomatic, it can be detected in the laboratory using the beryllium lymphocyte proliferation test (BeLPT) (Saltini et al. 1989; Rossman 2001). The BeLPT measures the proliferation of lymphocytes obtained from peripheral blood in the presence of soluble beryllium salts. Although regarded as the best tool for identifying beryllium-sensitized individuals, results may vary within and between laboratories (Deubner et al. 2001). Current criteria for diagnosis of CBD include the evidence of beryllium sensitization in the presence of non-caseating granulomas and/or mononuclear cell infiltrates in lung tissue (Newman et al. 2005).

Dermal exposure

Evidence suggests that skin contact with beryllium materials, including salts (Curtis 1951) and particles (Tinkle et al. 2003), are relevant to the development of beryllium sensitization. Historically, emphasis has been on the control of inhalation exposures to below the occupational exposure limit of 2 μg beryllium/m^3 of air; however, compliance with this mass-based exposure limit has proven ineffective in significantly reducing the occurrence of beryllium sensitization and CBD (Kreiss et al. 1996; Eisenbud 1998). The continued occurrence of beryllium sensitization and CBD may partially reflect inadequacy in the current occupational exposure limit for inhalation of beryllium. However, prevalences of sensitization and CBD at a copper-beryllium alloy finishing facility were similar to prevalences observed in other beryllium production facilities despite historical airborne beryllium exposure levels an order of magnitude below 2 μg beryllium/m^3 (Schuler et al. 2005). Thus, a model to describe beryllium exposures leading to adverse health effects is that skin exposure may be sufficient to cause an immune response (i.e., beryllium sensitization), while inhalation exposure even at levels below 2 μg beryllium/m^3 may be necessary for manifestation of lung disease (i.e., CBD).

Levels of skin exposure to beryllium salts, metal, oxides, alloys, and other beryllium-containing compounds have not been evaluated in the workplace. Skin as a route of exposure to poorly soluble particles of beryllium is highly plausible. For example, Tan et al. (1996) observed that poorly soluble titanium dioxide particles can penetrate intact human skin. Tinkle et al. (2003) observed in vitro that polystyrene latex spheres <1 μm in diameter, when coupled with flexing motion, can penetrate intact human skin. It should be noted that an upper bound size limit for particle penetration of skin may only apply to intact skin. It is not unreasonable that particles >1 μm in diameter that come into contact with damaged (e.g., open cuts or abrasions) or otherwise compromised (e.g., diseased) skin can cross the skin barrier. Note that CBD cases at a copper-beryllium alloy finishing facility were more likely to have reported ulcers or small craters in the skin, compared to employees without disease (Schuler et al. 2005). Skin exposure to soluble beryllium salts can cause beryllium sensitization in humans (Curtis 1951), and evidence suggests that skin contact with poorly soluble beryllium oxide particles can cause beryllium sensitization in mice (Tinkle et al. 2003).

Beryllium-containing materials vary widely in terms of their physicochemical properties, including particle size, morphology, surface area, and chemistry (Stefaniak et al. 2003, 2004). In turn, bioavailability (i.e., the degree to which beryllium ions become available to the target organ following exposure), which may be pertinent to the risk of beryllium sensitization and CBD, also varies widely among beryllium-containing materials. Beryllium salts (sulfate, chloride, fluoride, and others) are highly soluble and may induce sensitization (Curtis 1951), but are not commonly considered to cause CBD. Beryllium particles (metal, oxides, alloys, and others) are relatively insoluble and may be retained in the body for years, a condition which is sufficient for the formation and growth of granulomas (Stefaniak et al. 2003). In vitro studies of the dissolution of beryllium from particles using an extracellular simulant lung fluid (Finch et al. 1988), canine alveolar macrophages (Eidson et al. 1991), a phagolysosomal simulant fluid (Stefaniak et al. 2005), and a murine macrophage cell line model (Day et al. 2005) indicate that beryllium may become bioavailable following exposure.

To account for the contribution of both the inhalation and dermal routes to bodily beryllium exposure, improved monitoring techniques are needed. Potentially, biological monitoring of beryllium or beryllium derivatives in biological fluids could be used to assess total bodily exposure. Early attempts at biological monitoring for beryllium observed that beryllium levels in urine were indicative of exposure, but did not

correlate to exposure history or severity of disease (Klemperer et al. 1951; DeNardi et al. 1953; Stoeckle et al. 1969). However, recent advances in analytical chemistry methods have greatly improved the feasibility of biological monitoring for beryllium (Wegner et al. 2000; Apostoli and Schaller 2001). Using inductively coupled plasma-mass spectroscopy, Apostoli and Schaller (2001) demonstrated that levels of airborne beryllium correlated with levels of urinary beryllium among metallurgical workers. These data hold promise for development of validated biological markers that account for external exposure via inhalation and dermal contact with beryllium, internal exposure, and biologically-effective dose.

Immunology and genetics

Immunologic and genetic factors are pertinent to the development of beryllium sensitization and CBD. The beryllium-stimulated immune response is characterized by the involvement of a Major Histocompatibility Class II-restricted, CD4+ T helper 1 cell response. Antigen presentation to the T cell occurs via Human Leukocyte Antigen (HLA) molecules on the surface of antigen-presenting cells, in the case of the lung, macrophages and, in the case of the skin, Langerhans cells (Abbas et al. 2000). The involvement of HLA molecules implies that an HLA-T cell receptor interaction occurs, evidence for which is the demonstration that in vitro the beryllium-specific proliferative response can be blocked by anti HLA-antibodies (Saltini et al. 1989; Fontenot et al. 1998; Rossman 2001). A beryllium-specific clonal expansion then occurs that is driven by proinflammatory cytokines (TNF-α and IL-6) (Saltini et al. 1989; Tinkle and Newman 1997).

The finding that the beryllium-specific proliferative response can be blocked by anti-HLA-antibodies prompted molecular epidemiologic investigation of HLA-DP, DQ and DR DNA-sequence variants. The most closely associated haplotypes are those of HLA-DPB1 that code for a glutamic acid residue at the 69th position (E69) in the amino acid sequence of the mature protein (Weston et al. 2005, in press). The HLA-DPB1 gene family currently has 113 known DNA-sequence variants (http://www.ebi.ac.uk/imgt/). Thirty-nine variants code for E69 (GAG), 69 code for a lysine residue at the 69th position (AAG), and five code for an arginine residue at the 69th position (AGG). It appears that HLA-DPB1 haplotypes most closely associated with CBD code for HLA molecules that have relatively intense negative charge in and around the binding groove of the molecules (Snyder et al. 2003), suggesting that HLA molecules may readily bind positively charged beryllium ions. In addition, there is some evidence implicating an A/G polymorphism (TNF-α-308*02) in the promoter region of TNF-α (Saltini et al. 2001).

Summary statement

The use of control technologies (i.e., engineering, administrative, and respiratory protective equipment) to reduce inhalation exposures to below 2 μg beryllium/m^3 has not significantly reduced the occurrence of beryllium sensitization and CBD. The continued prevalence of beryllium sensitization and CBD may be due, in part, to unchecked skin exposure to beryllium-containing particles. We hypothesize that skin exposure to beryllium may be sufficient to cause sensitization, while inhalation is necessary for progression to lung disease. In light of our current understanding of the multiple exposure and immune pathways that may lead to sensitization and disease, a prudent approach is to assess and minimize both skin and inhalation exposures to beryllium in the workplace.

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