Beryllium: a paradigm for occupational lung disease and its prevention

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In this issue of the journal, Van Dyke and colleagues have shown that the supratypic genetic marker, HLA-DPB1(E69), has an additive and independent contribution with beryllium exposure to cell-mediated beryllium sensitisation and chronic beryllium disease in a cohort at a US nuclear weapons plant.[1] This finding of statistical independence between required beryllium exposure and genetic characteristics is quantitatively consistent with an earlier finding in a small beryllia ceramics operation,[2] and is extended by a concurrent publication in a second, larger nuclear weapons plant population.[3] In the latter case–control study, Van Dyke *et al* showed that the subset of rare HLA-DPB1(E69) alleles (non-*02), most with greater electronegativity in the antigen-binding groove,[4] conferred much higher risk of sensitisation and disease than the more common *02 HLA-DPB1(E69) genotypes: Both sensitisation and chronic beryllium disease risks were equally associated with genotype, but these two health outcomes differed with respect to exposure risk. Cumulative and average lifetime beryllium exposures were associated with chronic beryllium disease but not with beryllium sensitisation. Other recent studies of newly exposed beryllium workers demonstrate that sensitisation often occurs within months of employment, presumably before a beryllium lung burden sufficient for chronic beryllium disease is attained.[5–7] Although the Van Dyke paper in this issue did not have sufficient numbers to analyse beryllium sensitisation and beryllium disease cases separately, it showed compatible results, with the beryllium-sensitised cases having much lower indices of beryllium exposure compared with the chronic beryllium disease cases. The inference of these two Van Dyke papers is that early and repeated screening for beryllium sensitisation during employment, followed by curtailing further beryllium exposure among those sensitised, can lessen the risk of chronic beryllium disease.

These beryllium gene–environment studies are unique among the occupational lung diseases because we understand the immunological basis of the hypersensitivity lung disease and have a non-invasive blood test, the beryllium-specific lymphocyte proliferation test, which demonstrates that acquired sensitisation is a disease precursor. Genetic predisposition for disease and sensitisation was first shown nearly two decades ago on the basis of anti-HLA-DP-specific antibodies blocking the beryllium-specific lymphocyte proliferation test.[2] The findings of statistically independent genetic and beryllium exposure risks are not surprising, since chronic beryllium disease does not occur without beryllium exposure and occurs in persons without the HLA-DPB1(E69) marker, and there is no reason to assume that genetic risk and exposure risk correlate in the workforce. In other words, work in historically high-risk processes, such as beryllium machining, is not associated with immune response genes.

Understanding the quantitative relation between beryllium exposure and beryllium-related health outcomes has been slower than understanding the genetic risks. Early epidemiological findings established process-related risks of sensitisation and disease, but higher air exposures were not always associated with risk.[2] This motivated work on the physicochemical characteristics of different beryllium materials, such as particle size, surface area and solubility in different biological fluids.[2] The two Van Dyke papers benefited from more sophisticated exposure assessment using historical air data from a variety of facilities, probably lowering exposure misclassification. Similarly, exposure–response correlations have been found in a study of short-term workers in primary production of beryllium materials using personal lapel beryllium concentrations for reconstructing airborne historical exposures, in contrast to the area samples used to estimate exposures for earlier exposure–response evaluations in the US nuclear weapons facilities. Upcoming exposure–response studies in the primary production industry will also adjust beryllium exposures for physicochemical and other exposure characteristics. Finally, lowering beryllium air exposures did not prevent sensitisation early in employment.[2 5–7]

Prevention of beryllium sensitisation required refamiliarisation with work in the 1950s, which showed that a delayed sensitivity response could be elicited by skin patch testing in beryllium-naive subjects.[2] Subsequently, greatly reduced beryllium sensitisation rates were shown after multi-faceted interventions that included skin protection.[5–7] Whether lowering of beryllium sensitisation rates, in conjunction with removal from beryllium exposure, will lower chronic beryllium disease risk remains to be demonstrated. The pertinence of skin protection for preventing beryllium sensitisation has become a paradigm for other immunological lung diseases, such as isocyanate asthma, in which skin and clothing stains are associated with the risk of new chest symptoms.[8] A plethora of animal experiments have now found skin sensitisation by agents associated with asthma and other diseases, such as isocyanates, latex, 3-amino-5-mercapto-1,2,4-triazole, trimellitic anhydride, peanut antigens and diacetyl. Skin protection as a preventive intervention may be particularly pertinent to low molecular weight compounds and submicron sensitising dust exposures.

To date, beryllium studies have contributed to conceptual advances in occupational lung disease with gene–environment studies, more sophisticated treatment of historical air exposures, elucidation of dermal sensitisation in lung disease, and natural history of sensitisation and disease. Other contributions of interest include demonstration that cumulative sensitisation risk is much greater than cross-sectional risk,[9] the continuing discovery of neighbourhood cases outside the factory gates[10] and the need to consider unrecognised beryllium exposure in some cases of sarcoidosis. In 2012, three transgenic knock-in mice with human HLA-DPB1 alleles of differing genotype risk of sensitisation will be commercially available for the scientific community[11]; this will enable

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experimental examination of many questions regarding exposure dose rates, beryllium type and even novel treatment approaches.

Perhaps most important is the paradigm that beryllium studies offer for occupational health practice and health effects prevention: Medical surveillance for risk factors has allowed us to identify preventable risk factors, such as specific jobs or work processes, even when we do not have protective occupational exposure limits in place.[2 12] Moreover, surveillance with the beryllium-specific lymphocyte proliferation test has demonstrated the failure of relying solely on reducing airborne beryllium concentrations through engineering interventions and the considerable success of more comprehensive intervention including protecting skin from beryllium exposure. Thus, a standards compliance approach and a hierarchy of controls approach were both insufficient for prevention of beryllium sensitisation and disease. Some in our professional community maintain that beryllium-specific lymphocyte proliferation test screening has not been shown to improve outcomes for workers found to be abnormal, for example, by exposure cessation. While true, it is unlikely that a randomised clinical trial of removal from exposure would be ethically feasible given the increasing evidence that cumulative or lifetime average exposure is related to chronic beryllium disease. In the meantime, occupational health professionals can serve primary prevention by analysing population-based screening data to establish risk factors in the workplace that deserve intervention. This surveillance function can also establish the effectiveness of those interventions, as has been done in the primary beryllium industry. Primary prevention warrants surveillance of screening results as we await more studies of the natural history of beryllium sensitisation, beryllium disease and the evolving approaches to their treatment, informed by the genetic characteristics that affect them.

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