

**Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health
NIOSH Board of Scientific Counselors**

Report from the Subcommittee on Beryllium Research

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Introduction

Beryllium research is at the confluence and forefront of several prominent streams of science and public policy: basic, clinical, and occupational and environmental research; the human genome project; medical ethics and the right to work. Interest in the health effects of beryllium, an element still essential in the semi-conductor, electronics, nuclear, and automobile industries as well as fire suppressant systems, spark-free and non-magnetic tools, and X-ray windows, dates to the 1930s. Harriet Hardy led important studies in the United States in the 1940s that pioneered understanding of the element's toxicity. As a result of Hardy's and others' work, exposure to beryllium was reduced, resulting in the virtual elimination of acute berylliosis. However, chronic beryllium disease (CBD) remains a problem and the relation between beryllium and cancer has not been fully elucidated. Work has focused recently on trying to find predictors of CBD. Recently, some alleles of the human gene HLA-DPB1 have been identified as predictors of sensitization to beryllium. Some would assert that if these were strong predictors of disease, they should be sought in workers before exposure to beryllium to indicate the risk. In addition, for several years, researchers have tried to develop a test that could predict CBD in exposed workers. Finally, the US Department of Energy has recently established its action limit for airborne beryllium at $0.2 \mu\text{g}/\text{m}^3$, below the OSHA permissible exposure limit (PEL) of $2 \mu\text{g}/\text{m}^3$ and the NIOSH recommended exposure limit (REL) of $0.5 \mu\text{g}/\text{m}^3$.

These policy, practice, and research forces come to bear on NIOSH's research on beryllium. Beryllium research also exemplifies important intra-NIOSH, inter-agency, and labor-management matters. Assignment, coordination and accountability for projects within NIOSH; relationships with OSHA, NIEHS, Department of Defense, Department of Energy, and NIH as well as with industry and workers, and communications are some of the matters at hand. The latter arena is large, involving communications with government, labor, industry, and the general public about science, risks, protection, and principles.

The NIOSH beryllium research program has included studies in a wide range of disciplines including epidemiology, control technology, exposure assessment, industrial hygiene, immunology, and genetic research. In epidemiology studies, NIOSH researchers have collaborated with Brush Wellman Inc. to follow a cohort of beryllium industry workers with a goal of developing exposure-response information that predicts hazards of beryllium sensitization and disease. In this collaboration, Brush Wellman has provided NIOSH with results from screening questionnaires and lymphocyte proliferation tests (LPT) for analysis. NIOSH and Brush Wellman have also collaborated in industrial hygiene and exposure assessment studies to determine concentrations and particle size distributions of airborne beryllium dust and to identify appropriate worker protection measures in an effort to prevent future disease. Independent from Brush Wellman, NIOSH is conducting genetic analyses on a cohort of current and former workers in an effort to understand the genetic basis of chronic beryllium disease.

In other NIOSH studies, a case-control study has been performed to investigate the relationship between level of beryllium exposure and lung cancer. The use of control technology for reducing airborne concentrations of ultrafine beryllium particles has been examined in one NIOSH

project. In other projects, beryllium exposures and control methods are being studied in industries downstream from the beryllium production industry, and NIOSH investigators have studied take-home exposures among machine shop workers. Researchers have also investigated the importance of dermal exposures among beryllium workers, and are investigating whether dermal exposure can lead to sensitization to beryllium. Finally, NIOSH has funded two cooperative agreements with extramural researchers to investigate beryllium exposure-response relationships and the natural history of the disease.

Formation of the Subcommittee

In the autumn of 2000, the Subcommittee on Beryllium Research was established by James A. Merchant, MD, Chair of the Board of Scientific Counselors (BSC) of NIOSH. The members were: Linda Hawes Clever, M.D. (Chair), James M. Melius, M.D., Dr.P.H., William B. Bunn, M.D., Barbara A. Silverstein, Ph.D., John M. Dement, Ph.D., Neil A. Holtzman, M.D., M.P.H. (Consultant)

The charge to the Subcommittee was

“The Subcommittee on Beryllium Research will examine the internal NIOSH program in beryllium research and develop recommendations on strengths, weaknesses, appropriateness and effectiveness. The Subcommittee may also: 1) identify gaps in the current program and recommend priority areas for additional research and activities, including prevention interventions, e.g. control technology; 2) examine the ethical issues associated with research on genetic susceptibility to beryllium exposure and assess the implications for future NIOSH genetic susceptibility research; 3) consider the appropriateness and effectiveness of communications to current and potential employees about issues directly and indirectly related to NIOSH efforts; 4) review the current model NIOSH/industry collaboration in beryllium research and develop a template for future NIOSH collaborations with the private sector; and 5) other issues that the subcommittee identifies. The subcommittee will prepare a report for the full Board for their deliberations and recommendations to NIOSH.”

The charge was clarified via conference calls including with Linda Rosenstock, MD, MPH, then Director of NIOSH, and email. During this period, the Subcommittee, with the able assistance of James Stephens, PhD, Senior Scientist, and Kathleen Rest, PhD, then Deputy Director of Program, designed and refined questions to ask investigators. After answers had been received and distributed to the Subcommittee, it met on November 22, 2000 to assimilate information and, not surprisingly, to ask more questions. An additional list of questions was distributed to investigators. The committee was again struck with investigators' wisdom and thoroughness. The Subcommittee met on March 13, 2001 with investigators for their presentations, a conference call with Lee Newman, MD, a presentation by David Deubner, MD, Chief Medical Officer of Brush Wellman Inc., and an open forum with investigators. NIOSH investigators who presented information were Mike Colligan, Ph.D., Gayle DeBord, Paul Henneberger, Sc.D., Patrick Hintz, Mark Hoover, Ph.D., Kay Kreiss, M.D., Erin McCanlies, Ph.D., Mike McCawley,

Ph.D., Christine Schuler, Ph.D., John Sheehy, Sally Tinkle, Ph.D., Elizabeth Ward, Ph.D., and Ainsley Weston, Ph.D.

Following the March 2001 meeting, the Subcommittee developed preliminary conclusions and distributed responsibility for writing sections of the report. Over the following months, the Subcommittee conducted numerous discussions by conference call, and on several occasions followed up with NIOSH staff to clarify key issues. In February 2002, the full Board of Scientific Counselors was asked to review and comment on the initial draft report of the Subcommittee. The final draft report was completed in June 2002, and was sent to the BSC for its comments and discussion at the June 27, 2002 BSC meeting. The final report was completed in October, 2002.

Executive Summary and Recommendations

Overall, the Subcommittee was impressed with NIOSH research on beryllium, especially the investigators' drive and productivity. The Subcommittee enthusiastically thanks the researchers, staff, and indeed all of NIOSH for the ability to generate such outstanding work that affects the health of workers and our society as a whole. Brush Wellman participation has also been exemplary.

The subcommittee's conclusions and recommendations regarding beryllium center on improved communications to all affected and interested parties, worker protection and involvement in projects, genetic susceptibility research, completion of research protocols in a timely manner, and comprehensive definition of the size of the work force exposed to beryllium. On a more global scale, the subcommittee recommendations focus on ways to choose and coordinate projects, to set priorities, and to assure accountability and communication between Federal safety, health, and environmental agencies. A listing of specific recommendation follows.

General Recommendations

1. Given the nature of beryllium related diseases and the complexity of NIOSH research, there should continue to be high level initial oversight and reviews every two to five years by NIOSH leadership, the institutional review board (IRB) and the BSC. To supplement the existing mechanism, for example, the Director of NIOSH could appoint a senior scientist to coordinate resources and establish accountability for interdisciplinary and inter-Divisional projects.
2. Continued partnership of NIOSH, industry, and labor is needed for the conduct of research on beryllium. This research should be conducted according to tripartite mechanisms specified in the NIOSH study regulations (Part 85a of Title 42 of the Code of Federal Regulations), with worker involvement at the top level of decision-making.
3. When research results suggest a previously unreported workplace hazard, the Director should notify all appropriate Federal agencies including DOD, DOE, NIH, EPA, and other parts of CDC so that potentially harmful downstream effects can be studied and monitored efficiently.
4. NIOSH, and other appropriate organizations, should work together to encourage industries in which exposure to beryllium is discretionary to discourage use of beryllium when less hazardous alternatives are available.

Section I: Research Programs

I.A. General Research Recommendations

1. Assure timely, effective communications of research findings and other important information with affected and interested parties.
2. NIOSH should continue to review and evaluate the beryllium research program on a periodic basis to develop better approaches to coordinate the research program where problems are noted. The NIOSH research program is complex, involving many intramural and extramural collaborators, which makes program coordination both essential and difficult.

I.B. Recommendations Regarding Research Priorities

1. NIOSH research efforts can be better guided if the size of the workforce exposed to beryllium is defined. Estimates vary enormously because different data sets or assumptions are used; primary and secondary users and recyclers may not be fully counted; and workers formerly exposed are rarely considered.
2. **Downstream Exposures.** The subcommittee recommends that NIOSH expand its research program to assess better the risks and necessary control measures for these downstream users, and to encourage industries to substitute other less hazardous materials for beryllium when feasible. In addition to mining, production, and downstream users such as major manufacturers, there are many other workplace settings where beryllium exposures may be a problem (e.g., workplace exposures from dental implants, automotive parts, or recycling of electronic equipment).
3. **Control Technology.** NIOSH should examine its recommended exposure limit (REL) of 0.5 $\mu\text{g}/\text{m}^3$ to determine whether it is sufficient, and, if appropriate, forward a recommendation to OSHA to lower the permissible exposure limit (PEL) of 2 $\mu\text{g}/\text{m}^3$. Given the potential for adverse health effects at very low levels of exposure to beryllium and the difficulties posed by reliance on personal protective equipment, an expanded research effort is needed to develop and evaluate better engineering control measures for beryllium production, processing, and downstream users, including recycling.
4. **Long-term Follow-up of Exposed Workers.** We need to understand better the long-term consequences of sensitization to beryllium including such issues as progression of chronic beryllium related disease after cessation of exposure and the relation of sensitization to risk for lung cancer. Treatments for CBD need thorough evaluation.
5. **Exposure Characteristics.** Results of environmental and biological testing need to be available swiftly because of the high risk to workers and the need to intervene with education, control technology, and personal protective equipment. The relationship between skin exposure and sensitization and/or disease progression needs to be evaluated, as does the

role of ultrafine particulates. New and direct reading methods of beryllium determination, such as colorimetric swipe tests, need development and evaluation.

6. **Sensitization Testing.** The reliability and predictive value of the lymphocyte proliferation test (LPT) should be evaluated. Other markers of susceptibility, such as the utility of the TNF-a-308*2 marker and the HLA-DRArg-74 marker, need to be developed (Saltini, C.; Richeldi, L.; Losi, M.; Amicosante, M.; Voorter, C.; van den Berg-Loonen, E.; Dweik, R.A.; Widemann, H.P.; Deubner, D.C.; Tinelli, C. *Eur Respir J.*, 2001; 18:677-684). In the meantime, LPT should continue to be used.
7. The timing and methods by which workers are informed about sensitization should be defined.

Section II. Genetics: Epidemiologic and Ethical Issues

1. Since there is little hope in the near future of identifying who will get chronic beryllium disease (CBD) at the current maximum permissible exposure levels, efforts to reduce exposure of all workers should continue. At the present time, there appear to be some legitimate uses of beryllium for which no substitute can be found. However, discretionary uses should be discouraged.
2. Until efforts succeed to lower beryllium exposure to the point at which no CBD occurs, NIOSH research efforts to identify alleles that increase genetic susceptibility should continue.
3. NIOSH should conduct its research in a manner that complies with CLIA certification even though such certification is not required. This is especially important when results of genetic tests for susceptibility to beryllium sensitization or any other laboratory results are given to study participants.
4. With the involvement of workers, NIOSH should make greater efforts to define when an association between a genetic marker on the one hand and beryllium sensitization and/or CBD on the other is sufficiently strong to be reported either on request to individual workers or to all workers. One criterion would be that most workers would consider it when making employment decisions. Involvement of workers is consistent with the tripartite review process.
5. Individual results of tests of gene markers that are obtained in NIOSH research studies are being, and should continue to be provided to workers who request them. The results must be communicated to workers in a manner that clearly defines the limits of the test and conclusions that may be drawn. Workers should be given the opportunity to request their results at the time they consent to participate in the study. In addition, they should continue to be told that the overall results would be communicated when sufficient data have been

collected and analyzed to be confident of the strength of association. Usually, this will be at the conclusion of the study.

6. In conducting research on genetic susceptibility, NIOSH should continue to study and evaluate how best to communicate the risks of beryllium exposure and the implications of results of tests for susceptibility to CBD.
7. The relationship between LPT sensitization and genetic predisposition/genotype should be clarified.

Section III. Communication of Potential Health Risks of Beryllium

1. Distribute a NIOSH Alert focused on industries where beryllium exposure is most likely. There should also be NIOSH Alerts aimed at downstream users, including recycling and disposal industries and workers.
2. NIOSH should communicate research findings to other domestic agencies (OSHA, EPA, DOE, and other parts of CDC), internationally (WHO, UN, IARC, ILO), and to beryllium-using manufacturers and other industries with exposures. Communication should include a full discussion of health risks that exist at the current PEL, protective equipment, engineering controls, and the current status of genetic testing.
3. NIOSH in concert with Brush Wellman and other manufacturers should review the current communication programs to workers and downstream users and make changes as appropriate.
4. NIOSH should explore and evaluate better methods of communicating study results with significant health findings to workers and affected industries.

Section IV: NIOSH/Industry Collaboration in Beryllium Research

1. All collaborative research should follow NIOSH study regulations that contain provisions for tripartite participation (government, labor, and industry) at all levels of project initiation, execution, review, and information dissemination. These regulations should also contain NIOSH provisions concerning proprietary or trade secret information. All memoranda of understanding (MOUs) should incorporate these by reference.
2. Collaborative efforts must not impede or delay implementation of prudent public health actions to eliminate or minimize worker risks, including sampling of worker exposure and notification. This is especially important when data might point to a causal connection but are not yet sufficient to draw firm conclusions. Occasionally public health action must be undertaken using imprecise or sparse data, while research continues.

3. Collaborative research arrangements must not hinder or modify NIOSH's statutory access to the workplace or information derived from the workplace, or limit the ability of NIOSH to alter or change its research program or direction. The current MOU seems to suggest that collaborating parties must consent to an *increase* of funding; this wording should be corrected in the future.

I. Research Programs

The subcommittee was impressed with the current NIOSH research program on beryllium, both in terms of the scientific quality of the work and the progress made to date. The cooperative and close interaction with Brush Wellman has also been beneficial to the quality and achievements of this research.

The subcommittee believes that beryllium research deserves priority within NIOSH's overall research effort and that better oversight would facilitate management of the program including securing necessary resources. Based on the scope of the program, the nature of the collaborative effort with Brush Wellman, and the need to ensure coordination of efforts and resources among the participating divisions, the subcommittee recommends that NIOSH develop a better approach to coordinate the research program through the Office of the Director. In particular, need for quick yet reliable results of research involving workers' exposure, sensitivity to beryllium, and susceptibility to disease compels NIOSH to designate and fund the means for deciding which specimens should be analyzed first, and expanding testing capacity when necessary. This is important, since beryllium is currently an essential component in some industries, but can lead to chronic beryllium disease and death.

Other areas of urgency include developing a surveillance system to study the health effects of beryllium in workplace settings other than mining, production, and downstream users such as major manufacturers. Because beryllium is used in a variety of products, including dental implants¹, automobile parts, aerospace products, telecommunications equipment, and computers, there is a substantial possibility of beryllium exposure to workers in fields seemingly unrelated to the beryllium industry. There is little published information in this area.

NIOSH may also need to examine its recommended exposure limit (REL) to determine if it is sufficiently protective. The current REL of $0.5 \mu\text{g}/\text{m}^3$ is below the OSHA permissible exposure limit (PEL) of $2 \mu\text{g}/\text{m}^3$, but above the action limit of $0.2 \mu\text{g}/\text{m}^3$ set by the US Department of Energy for its workers. NIOSH should consider recommending to OSHA that it lower the current PEL.

It is also essential that analyses of biological and environmental samples be carried out quickly to provide timely information for developing appropriate prevention programs. Improving control technology and personal protective equipment also require greater attention, since the time is so short during which sensitization to beryllium occurs.

In addition to these areas, the Subcommittee calls attention to the need to reevaluate the lymphocyte proliferation tests (LPT) as a screen for assessing sensitization: Is this test reliable? What is its predictive value? Are other tests preferable and should they be developed? In

¹ The U.S. Occupational Safety and Health Administration issued a Hazard Identification Bulletin in April, 2002, "Preventing Adverse Health Effects from Exposure to Beryllium in Dental Laboratories" (OSHA, HIB 02-04-19)

addition, there is a need to clarify the relationship between LPT sensitization and genetic predisposition. Further basic questions include: What is the pathophysiology of chronic beryllium disease and possible beryllium-associated cancers? How is beryllium absorbed and does the pathway affect disease development?

The subcommittee has a number of recommendations for research priorities, listed here in order of priority. Many of these recommendations overlap with current program research plans; some address gaps in the beryllium research program.

A. General Research Recommendations

1. Assure timely, effective communications of research findings and other important information with affected and interested parties.
2. NIOSH should continue to review and evaluate the beryllium research program on a periodic basis to develop better approaches to coordinate the research program where problems are noted. The NIOSH research program is complex, involving many intramural and extramural collaborators, which makes program coordination both essential and difficult.

B. Recommendations Regarding Research Priorities

1. NIOSH research efforts can be better guided if the size of the workforce exposed to beryllium is defined. Estimates vary enormously because different data sets or assumptions are used; primary and secondary users and recyclers may not be fully counted; and workers formerly exposed are rarely considered.
2. **Downstream Exposures.** The subcommittee recommends that NIOSH expand its research program to assess better the risks and necessary control measures for these downstream users, and to encourage industries to substitute other less hazardous materials for beryllium when feasible. In addition to mining, production, and downstream users such as major manufacturers, there are many other workplace settings where beryllium exposures may be a problem (e.g., workplace exposures from dental implants, automotive parts, or recycling of electronic equipment).
3. **Control Technology.** NIOSH should examine its recommended exposure limit (REL) of 0.5 $\mu\text{g}/\text{m}^3$ to determine whether it is sufficient, and, if appropriate, forward a recommendation to OSHA to lower the permissible exposure limit (PEL) of 2 $\mu\text{g}/\text{m}^3$. Given the potential for adverse health effects at very low levels of exposure to beryllium and the difficulties posed by reliance on personal protective equipment, an expanded research effort is needed to develop and evaluate better engineering control measures for beryllium production, processing, and downstream users, including recycling.

4. **Long-term Follow-up of Exposed Workers.** We need to understand better the long-term consequences of sensitization to beryllium including such issues as progression of chronic beryllium related disease after cessation of exposure and the relation of sensitization to risk for lung cancer. Treatments for CBD need thorough evaluation.
5. **Exposure Characteristics.** Results of environmental and biological testing need to be available swiftly because of the high risk to workers and the need to intervene with education, control technology, and personal protective equipment. The relationship between skin exposure and sensitization and/or disease progression needs to be evaluated, as does the role of ultrafine particulates. New and direct reading methods of beryllium determination, such as colorimetric swipe tests, need development and evaluation.
6. **Sensitization Testing.** The reliability and predictive value of the lymphocyte proliferation test (LPT) should be evaluated. Other markers of susceptibility, such as the utility of the TNF-a-308*2 marker and the HLA-DRArg-74 marker, need to be developed (Saltini, C.; Richeldi, L.; Losi, M.; Amicosante, M.; Voorter, C.; van den Berg-Loonen, E.; Dweik, R.A.; Widemann, H.P.; Deubner, D.C.; Tinelli, C. *Eur Respir J.*, 2001; 18:677-684). In the meantime, LPT should continue to be used.
7. The timing and methods by which workers are informed about sensitization should be defined.

II. Genetics: Epidemiologic and Ethical Issues

The first part of this section will summarize the current state of knowledge of the genetics of CBD. In the second part, we turn to ethical issues that have arisen in NIOSH research. Finally, we examine future possibilities for research and suggest ways to provide results.

Epidemiologic considerations: The current state of knowledge

In 1993 Richeldi et al. reported that the Glu-69 HLA-DPB1 allele (hereafter Glu-69) was associated with an increased risk of chronic beryllium disease among exposed workers (Richeldi, L.; Sorrentino, R.; Saltini, C. *Science*, 1993; 262:242-244). The Glu-69 allele frequency in the population is 22%, giving a combined frequency of homozygotes and heterozygotes of 39% under Hardy-Weinberg equilibrium. Using standard epidemiological formulas (Khoury, M.J.; Newill, C.A.; Chase, G.A. *Am J Pub Hlth* 1985; 75:1204-1208) and a probability of CBD of 5% among those exposed, an odds ratio of 10 and a Glu-69 genotype frequency of 40%, the positive predictive value (PPV) of a test for Glu-69 is 11%, and the risk of CBD attributable to Glu-69 is 78% (Saltini, C.; Richeldi, L.; Losi, M.; Amicosante, M.; Voorter, C.; van den Berg-Loonen, E.; Dweik, R.A.; Widemann, H.P.; Deubner, D.C.; Tinelli, C. *Eur Respir J*, 2001; 18:677-684). In 1999, researchers in the Department of Energy's Los Alamos national laboratory reported that some Glu-69 HLA-DPB1 alleles were associated with greater susceptibility to CBD than others. (Wang, Z.; White, P.S.; Petrovic, M.; Tatum, O.L.; Newman, L.S.; Maier, L.A.; Marrone, B.L. *J Immunol* 1999; 163:1647-1653.)

NIOSH research. The basis for NIOSH's genetic studies in beryllium workers was established in a Memorandum of Understanding (MOU) and an accompanying Statement of Work agreed to by Brush Wellman Incorporated (hereafter BWI) and NIOSH in 1998. Genetic studies were merely mentioned in these agreements but a Protocol² approved by NIOSH's Human Subjects Review Board (HSRB) in 1999, and an appendix to the Protocol, spelled out these and related studies in detail. Under the Protocol, BWI agreed to complete medical screening (including BeLPT) and clinical evaluation (bronchial lavage etc.) of current workers at its Tucson and Elmore plants ("Phase I"). NIOSH agreed to genotype current workers at the Tucson and Elmore plants and to perform blood BeLPTs and genotyping of former employees who had participated in a genetic association study (non-NIOSH) in 1992-94 ("Phase II"). In addition, NIOSH agreed to extend cross-sectional genotype characterization to all other Brush Wellman work forces ("Phase III")³ The objective of these studies is to examine the associations of Glu-69 HLA-DPB1 and other inherited variants with beryllium sensitization (as measured by BeLPT), and with the occurrence and progression of CBD.

² Study Protocol. Gene-Environment Interaction In Beryllium Sensitization And Disease Among Current And Former Beryllium Industry Workers. NIOSH, December 23, 1999. Hereafter referred to as Protocol.

³ Phases II and III were to be conducted by NIOSH independent of Brush Wellman, which did not want information from genetic analyses.

Phase I has now been completed and BWI is conducting another round of medical surveillance of current workers. NIOSH has completed genotyping of current and former employees at the Tucson and Elmore plants using restriction fragment length polymorphism (RFLP) assays for Glu-69 HLA-DPB1. It has also completed these assays on current workers at BWI's Reading plant. Genotyping of current and former employees at other plants has not yet been performed. NIOSH will perform allele-specific sequencing for sub-types of Glu-69 HLA-DPB1 alleles and study polymorphisms at other gene loci, but has done neither yet.

A recent report (Yucesoy, B.; Vallyathan, V.; Landsittel, D.P.; Sharp, D.S.; Matheson, J.; Burleson, F.; Luster, M.I. *Am J Indust Med* 2001; 39:286-291) regarding polymorphisms of the IL-1 gene complex and susceptibility to silicosis extended the genome project to other workplaces and substances. Thus, this is an opportune time to establish policies for research on genetic susceptibility to CBD since they may serve as models for studying other genetic susceptibilities to workplace exposures.

Ethical considerations: The current situation

Ethical issues of genetic testing in the workplace have achieved prominence in the past eighteen months:

- \$ Former President Clinton issued an Executive Order forbidding federal employment decisions based on protected genetic information. (Previously, 22 states had banned the use of genetic screening for making employment-related decisions).
- \$ The Equal Employment Opportunity Commission stopped Burlington Northern Santa Fe Railroad from testing for deletion in a gene on chromosome 17 that might "predispose" employees to carpal tunnel syndrome. Although the company said the tests were not required of the 125 workers who had submitted carpal tunnel claims and that no action or threat was made against persons who declined testing, the company requested that workers submit blood without explaining it would be used for genetic testing. Deletion in the gene on chromosome 17 is related to a rare condition, hereditary neuropathy with liability to pressure palsy, and not to carpal tunnel syndrome as it is usually described.
- \$ The American College of Occupational and Environmental Medicine reiterated its adoption of the Institute of Medicine's recommendations (1994) that genetic testing be entirely voluntary with informed consent and confidentiality of results. The IOM urged particular caution in interpreting pre-symptomatic and predictive test results. Such tests should, the IOM recommended, be accompanied by genetic counseling.

The major ethical considerations for NIOSH in its conduct of research on genetic susceptibility to CBD are the involvement of workers in planning and implementation and whether and how workers should be given their individual results.

Involvement of workers. The NIOSH Protocol was reviewed by the Project Leadership Team (described in the MOU) on which beryllium workers are represented. Organized labor is also

represented on the HSRB, but not beryllium workers. The staffs of the Paper and Allied Chemical Union and the Steelworkers Union also reviewed the protocol.

NIOSH staff conducted small group meetings at BWI work sites to introduce workers to the genetics study. The meetings lasted 1.0-1.5 hours and usually were attended by approximately 20 workers. During the course of the study NIOSH representatives have made periodic field visits to the BWI plants in part to answer worker questions about the research. The Subcommittee notes that there is frequent NIOSH-worker contact regarding the implementation of the Protocol.

In all cases, because of the complexity and uncertainty of the significance of findings, participation of workers in developing protocols and receiving results should be documented and their understanding evaluated.

Communicating individual results. The consent disclosure for NIOSH's genotyping Protocol states that the purpose is "to study how genes and type of exposure affect risk of disease." It adds, "We do not plan to send you your personal results, but you will receive a report of the overall results of the research." The NIOSH Human Subjects Review Board (HSRB)

“. . . felt that it was ill-advised to decide a priori that participants should be notified of their Glu-69 results. We decided, instead, to tell participants in the consent form of the uncertain status of the Glu-69 situation and to advise them of the risks associated with getting these results. We also informed them that we did not intend to give them these results. However, we did feel, as a federal agency, that we could not refuse to provide individuals with their own personally identifiable information if they insisted. Our obligation, in this case, would be to once again advise them of the risks of receiving ambiguous findings, the misinterpretation of which could have serious repercussions, and to advise them to reconsider. If they still requested their results at the end of the study, it was hoped that the analysis of the NIOSH data would allow us to give a more definitive explanation of the Glu-69/sensitization/berylliosis relationship. Under no conditions, however, would the Brush Wellman organization receive individually notifiable results of the Glu-69 analyses from NIOSH.”

The consent disclosure, and the letter sent to those who request individual results itemize the risks of receiving results, including employment and insurance discrimination, and laboratory error.⁴ NIOSH obtained a certificate of confidentiality for this study, so that a result could not be subpoenaed from NIOSH, but as the disclosure points out, "some insurance companies or employers may ask you for it."

Thus far out of about 1000 workers who consented to be genotyped, 44 have contacted NIOSH to discuss receiving their individual results. After receiving the letter described above, and in some cases having other conversations with NIOSH representatives, only 15 have requested their

⁴ The "Request for Result letter" says "(R)esearch results may not be as accurate as you would expect from a standardized commercial clinical laboratory...Before acting on your genetic result, you may want to have your test confirmed by a clinical genetic testing laboratory." The letter also noted, "Genetic testing in a clinical laboratory is usually accompanied by genetic counseling."

results. Eleven of these 15 are former workers. A NIOSH representative has attempted to telephone these 15 workers to see if they have further questions and has spoken with 6 of them thus far.

Although the Glu-69 HLA-DPB1 genotyping has been completed in the Tucson, Elmore, and Reading plants, NIOSH has not summarized the aggregate results for all workers. One reason is that additional longitudinal data is being collected; the magnitude of the association of the marker with beryllium sensitization or CBD has not yet been established. NIOSH is also considering a newsletter for workers regarding the research.

The Subcommittee has concerns about the readability and clarity of the disclosure form for consent. For instance, although the frequency of HLA-DPGlu-69 of 30-40% in the general population, and the overall risk of CBD of 12.2% with this “marker” are both indicated, the probability that as many as 70% of workers with an HLA-DPGlu-69 allele might never get CBD is not explicitly stated. As already noted, NIOSH representatives make field visits to BWI plants as part of this research, giving them the opportunity to discuss the research further with groups of workers or individual workers who ask questions.

In reply to its question about workers’ understanding about the information provided, the Subcommittee was told

NIOSH has not assessed comprehension in a quantitative fashion. On the basis of numbers and types of questions raised in meetings and one-on-one at both plant site and long distance, the comprehension appeared to be good. However workers in this plant [Elmore] may be unusual in that Brush Wellman conducts considerable education through its required safety meetings...@

The Subcommittee believes that workers’ comprehension of the genetic issues should be evaluated. Pre- and post-test counseling, and evaluation of that counseling, would be prudent when workers are given their individual results.

Future possibilities

It remains for NIOSH to complete RFLP testing for HLA-DPGlu-69 at BWI sites other than Tucson, Elmore, and Reading and to test subtypes of HLA-DPGlu-69 alleles and variants at other gene loci for associations with beryllium sensitization and CBD at all sites. Should the request for, and reporting of, individual results be handled differently in these cases? In both, consent has already been obtained and the procedure for subjects to obtain individual results on request has been defined. The Subcommittee does not think it appropriate to alter the consent process for reporting HLA-DPGlu-69 results to current and former workers from other plants whose specimens have not yet been analyzed. However, the Subcommittee believes that further consideration is needed for the reporting of subtypes of HLA-DPGlu-69 alleles and variants at other gene loci. In the Protocol, the NIOSH HSRB also made a distinction between HLA-DPGlu-69 and other markers.

“ . . . we will communicate individual results for HLA-DPGlu-69 at the conclusion of the study. NIOSH Human Subjects Review Board review at the conclusion of the study will inform whether we report personal results of other genetic analyses to participants, depending upon strength of associations (if any), independent confirmatory publications during the course of this research, and whether benefit would accrue to participants . . . (T)he likelihood that clinically interpretable information will arise from this study is low. (Protocol, p. 20)@

The Subcommittee concurs with HSRB that a key factor is “the strength of association” between specific genotypes and sensitization and/or CBD. If *no* association were found between the variants being studied and sensitization and/or disease, participants would be informed and findings would be explained, even though it would not aid them in their decision to be exposed to beryllium and would entail considerable expense in communication and counseling.

The protocol wisely concluded that the decision to report would result from “review at the conclusion of the study. (p. 20)” Only at the conclusion could the data be analyzed to assess the strength of association. (A data safety monitoring board could evaluate results on an ongoing basis but the numbers would probably be too small to be confident of the strength of association.) This was revised during the course of the study: workers who requested their individual results have been given them before the end of the study. Except when very strong associations are found before the conclusion of a study, which was not the case for HLA-DPGlu-69, the Subcommittee thinks that study protocols should be followed, and that exception made only after thorough review.

The Subcommittee also agrees with the HSRB that an “independent confirmatory publication” of an association found in NIOSH research enhances the advisability of reporting individual results.

Not every statistically significant association, however, will have practical implications. Although the association between HLA-DPGlu-69 and CBD is statistically significant, its predictive value is lower than many clinical tests. Fewer than 5% of workers exposed to beryllium are interested in receiving their results. Only about one-quarter of new hires by BWI avail themselves of the opportunity to be tested for HLA-DPGlu-69 without their employer’s knowledge.⁵

The Subcommittee believes it is appropriate to involve worker representatives, as well as the NIOSH HSRB, in deciding how to report possible associations to workers. They could provide the best answer to another criterion that should be used in deciding on the strength of the association: whether most workers would consider it in making a decision of employment in the beryllium industry.

⁵Per telephone conversation between Lynn Godmillow, genetic counselor at the Medical Genetics Department at the University of Pennsylvania, and Neil A. Holtzman, April 16, 2001.)

In considering how to report findings, there are two alternatives: (1) The association is essentially absent or is moderately strong, and should be available to individual workers who request it; (2) The association is strong enough so that it should be made available to all workers. The consent disclosure should describe these two alternatives, the criteria to be used in deciding among them, and the personnel involved in the decision. As part of the consent, workers should be asked whether, at the completion of the study, they want their individual results under alternative 1 or not.

It is possible that additional research, as planned by NIOSH, will discover HLA-DPB1 alleles in addition to or instead of the Glu-69 allele, or alleles at other gene loci, that will increase the risk of CBD more than does Glu-69 alone. If this happens, both workers and employers may have greater interest in an individual's genetic susceptibility to CBD.

Since NIOSH is already reporting individual results to workers, and results must be reliable, and since the NIOSH laboratory is not required to be certified under CLIA, the Subcommittee feels that NIOSH laboratory standards and practices should be consistent with privacy considerations and CLIA standards of excellence.

Recommendations

1. Since there is little hope in the near future of identifying who will get chronic beryllium disease (CBD) at the current maximum permissible exposure levels, efforts to reduce exposure of all workers should continue. At the present time, there appear to be some legitimate uses of beryllium for which no substitute can be found. However, discretionary uses should be discouraged.
2. Until efforts succeed to lower beryllium exposure to the point at which no CBD occurs, NIOSH research efforts to identify alleles that increase genetic susceptibility should continue.
3. NIOSH should conduct its research in a manner that complies with CLIA certification even though such certification is not required. This is especially important when results of genetic tests for susceptibility to beryllium sensitization or any other laboratory results are given to study participants.
4. With the involvement of workers, NIOSH should make greater efforts to define when an association between a genetic marker on the one hand and beryllium sensitization and/or CBD on the other is sufficiently strong to be reported either on request to individual workers or to all workers. One criterion would be that most workers would consider it when making employment decisions. Involvement of workers is consistent with the tripartite review process.

5. Individual results of tests of gene markers that are obtained in NIOSH research studies are being, and should continue to be provided to workers who request them. The results must be communicated to workers in a manner that clearly defines the limits of the test and conclusions that may be drawn. Workers should be given the opportunity to request their results at the time they consent to participate in the study. In addition, they should continue to be told that the overall results would be communicated when sufficient data have been collected and analyzed to be confident of the strength of association. Usually, this will be at the conclusion of the study.
6. In conducting research on genetic susceptibility, NIOSH should continue to study and evaluate how best to communicate the risks of beryllium exposure and the implications of results of tests for susceptibility to CBD.
7. The relationship between LPT sensitization and genetic predisposition/genotype should be clarified.

III. Communication of Potential Health Risks of Beryllium

Effective health communication involves communication to workers, unions, families, product purchasers, downstream users, community and recyclers/waste removal personnel. However, it is not clear if all miners/manufacturers with national/international scope have effective programs, nor is it clear whether there is compliance even if programs are in place. Beryllium is used in hundreds of ways, some by primary purchasers, others downstream users. Recyclers of cell phones, computers, and other electronic devices, dental technicians, and fabrication workers are likely not aware of the risks. Effective communication to downstream users and recyclers/waste disposal personnel is particularly difficult.

Therefore, an effective communication program involves outreach. Secondary users, and where possible, waste disposal companies need to be notified. Since the current PEL is not protective, it is most important to communicate in a timely fashion.

Recommendations

1. Distribute a NIOSH Alert focused on industries where beryllium exposure is most likely. There should also be NIOSH Alerts aimed at downstream users, including recycling and disposal industries and workers.
2. NIOSH should communicate research findings to other domestic agencies (OSHA, EPA, DOE, and other parts of CDC), internationally (WHO, UN, IARC, ILO), and to beryllium-using manufacturers and other industries with exposures. Communication should include a full discussion of health risks that exist at the current PEL, protective equipment, engineering controls, and the current status of genetic testing.
3. NIOSH in concert with Brush Wellman and other manufacturers should review the current communication programs to workers and downstream users and make changes as appropriate.
4. NIOSH should explore and evaluate better methods of communicating study results with significant health findings to workers and affected industries.

IV. NIOSH/Industry Collaboration in Beryllium Research

The NIOSH beryllium research program includes a high degree of collaboration with Brush Wellman Inc. In many respects, the level and degree of collaboration offers a model for similar work with industry groups. A memorandum of understanding (MOU) sets forth conditions, expectations, and parameters for collaboration. The Beryllium Subcommittee reviewed the MOU and discussed ongoing collaboration with investigators from both NIOSH and Brush Wellman. Both NIOSH and Brush Wellman reported that the MOU was working well and resulting in joint research efforts and results not easily attainable by one party working alone. The MOU is consistent with the National Occupational Research Agenda (NORA), which seeks to partner federal agencies with key stakeholders in priority areas in order to define better research needs and leverage resources for research in critical priority areas. The NIOSH beryllium research effort addresses several NORA areas including Surveillance Research Methods, Control Technology and Personal Protective Equipment, Exposure Assessment Methods, Allergy and Dermatitis, Special Populations at Risk, and Intervention Effectiveness Research.

While all parties reported that collaborative efforts were working well, the Subcommittee conducted a detailed review of the MOU using the NIOSH study regulations as the benchmark for tripartite collaboration. The beryllium MOU was considered as a possible model for NIOSH collaboration with industries, noting the following comments:

Comments

1. While workers or worker representatives have some representation as described in the MOU, this is only on the Project Leadership Team (PLT) and not on the Project Management Team (PMT). Consistent with NIOSH study regulations, the Subcommittee considered it important that workers be afforded true stakeholder status including involvement in all aspects of project conceptualization, execution, review, and dissemination of results.
2. Communication of results, as appropriate, should be arranged by prior agreement of affected parties. The MOU does not define clearly the information flow and should refer to the tripartite process, which requires review before, during, and after the study.
3. Function and authority of the PLT are vague. For example, the PLT is given project statements of work (SOW) for review only after approval of the PMT. It is not clear who has final authority to approve project SOWs.
4. Statements of work as well as increases or decreases in funding can be made only with prior written consent of the other party to the MOU. The MOU should be reworded to make it clear that NIOSH retains the right to enhance research programs where needed.
5. Treatment of proprietary information is addressed in the MOU, but its provisions could conflict with NIOSH study regulations. For example, page 4 of the MOU states that ---

“NIOSH has agreed to participate in the Program subject to the procedures specified in Part 85a of Title 42 of the Code of Federal Regulations.” However, the MOU also states in Section 12(A) concerning data collection, utilization, reports and publications: “It is expressly understood that these reports shall not be construed to provide for the release of proprietary information generated or provided in the performance of the SOW to any party which is not a party to the SOW”.

This additional sentence in the MOU is not needed if NIOSH study regulations are followed since detailed procedures for declaring, handling and releasing proprietary information. NIOSH study regulations should not be changed or modified in any way by the MOU. The extra provision in the MOU, as described in the sentence above, appears to have this potential. A more appropriate sentence would simply state that proprietary or trade secret information would be handled as specified in Part 85a of Title 42 of the Code of Federal Regulations.

6. Release of exposure and other information to plant management requires prior review by the PMT. The lack of worker representation on the PMT appears to exclude them from decisions made concerning data release.
7. The MOU states that the PMT will review papers and documents before any publication or release. Again, this process does not have worker representation.

The above comments and observations are not intended to imply any impropriety on the part of NIOSH or Brush Wellman in establishing the MOU or collaborative arrangements nor that NIOSH study regulations are not being followed. Indeed, this arrangement can be considered groundbreaking. In this spirit, the Subcommittee proposes that NIOSH consider the following recommendations in future collaborations.

Recommendations

1. All collaborative research should follow NIOSH study regulations that contain provisions for tripartite participation (government, labor, and industry) at all levels of project initiation, execution, review, and information dissemination. These regulations should also contain NIOSH provisions concerning proprietary or trade secret information. All memoranda of understanding (MOUs) should incorporate these by reference.
2. Collaborative efforts must not impede or delay implementation of prudent public health actions to eliminate or minimize worker risks, including sampling of worker exposure and notification. This is especially important when data might point to a causal connection but are not yet sufficient to draw firm conclusions. Occasionally public health action must be undertaken using imprecise or sparse data, while research continues.

3. Collaborative research arrangements must not hinder or modify NIOSH's statutory access to the workplace or information derived from the workplace, or limit the ability of NIOSH to alter or change its research program or direction. The current MOU seems to suggest that collaborating parties must consent to an *increase* of funding; this wording should be corrected in the future.

Appendix 1: Listing of NIOSH Beryllium Research Projects

<u>Project</u>	<u>Investigators</u>	<u>Division</u>
1 Epidemiology	Christine Schuler, Ph.D. Paul Henneberger, Sc.D. Kathleen Kreiss, M.D.	DRDS

The purpose of this research is to develop exposure-response information with a metric that predicts hazard of beryllium sensitization and disease. Previous work has shown that gravimetric beryllium measurements did not correlate with risk, although process-related risk suggested that other exposure characteristics likely conferred risk. An additional purpose is to define exposure-response relations for the substantial segment of the workforce (30-40%) with enhanced genetic susceptibility. Finally, with longitudinal follow-up of beryllium workers, this project will define cumulative incidence and natural history of sensitization and disease, including after employment cessation, as functions of exposure metrics (including skin exposure), genetic characteristics, and preventive interventions in the workplace.

2 Industrial Hygiene and Exposure Assessment	Mark Hoover, Ph.D. Paul Hewett, Ph.D.	DRDS
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This research provides data on the concentrations and characteristics of beryllium aerosols to which workers have been and are being exposed. Exposures by both the inhalation and dermal route are being studied. This information is used in the epidemiology studies to identify exposure-response relationships. It is also used to guide the development and implementation of improved methods for the primary prevention of exposure, sensitization, and disease. A critical focus is on determining the role of particle surface area, particle solubility, particle size, and particle number on the bioavailability of beryllium in the lung and in skin.

3 Genetic Factors	Ainsley Weston, Ph.D. Erin McCanlies, Ph.D.	HELD
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This study is providing insights into the genetic basis of beryllium sensitization and disease. An understanding of the mechanisms of sensitization and disease can then be used for primary and secondary intervention purposes (not simply issues of susceptibility). Conflicting information exists in published studies regarding the specific allelotypes implicated in the disease process. This study will identify the “target” alleles for scrutiny in mechanistic studies using a transgenic mouse.

4 **Immunopathology**

Sally Tinkle, Ph.D. HELD
Ann Hubbs, Ph.D.

During the last ten years, the beryllium industry has made major improvements in respiratory protection and engineering control technology design; however, the rate of disease has not declined. A hypothesis of the project is that dermal exposure to beryllium particles provides an alternative route for sensitization to beryllium. A coordinated series of laboratory experiments have shown penetration of particles into intact stratum corneum and stimulation of a beryllium-specific immune response by cutaneous application of beryllium. These data support the hypothesis that cutaneous exposure to beryllium particles can result in a beryllium-specific cellular immune response.

5 **Molecular Dynamics Simulations**

Eugene Demchuk, Ph.D. HELD
James A. Snyder, Ph.D.

A molecular modeling approach is being used to map the genetic markers of CBD on the HLA-receptor molecule and to better understand the molecular basis of the beryllium disease process. Preliminary analysis of a reconstructed model has revealed that all of the amino acid species so far known to be closely associated with CBD development are located at the antigen-binding groove of the molecule and instigate a highly negative electrostatic potential in the binding groove of the disease HLA.

6 **Extramural Activities**

Paul Henneberger, Sc.D. DRDS

NIOSH has had two cooperative agreements to investigate beryllium exposure-response relations and natural history of beryllium disease, funded by NIOSH with funds from an interagency agreement with the US Department of Energy (DOE). These 5-year cooperative agreements, initiated in 1995, were awarded to Ken Rosenman (Michigan State University, with collaborators Carol Rice at the University of Cincinnati and Milton Rossman at University of Pennsylvania), and Lee Newman (National Jewish Medical and Research Center, Denver, CO).

7 **Estimating the Number of Beryllium Workers**

Brent Doney, M.S., C.I.H. DRDS
Sandra Goe, M.S.
Paul Henneberger, Sc.D.
William Miller, M.S.

This project is estimating the number of workers exposed to beryllium in the U.S. Methods are being defined and applied to identifying both primary industry workers and downstream users. Results will facilitate specific interventions in other projects to increase awareness of beryllium disease and to reduce the incidence of disease.

8 **Documentation and Evaluation of Beryllium Exposures and Control Techniques**

Keith Crouch, Ph.D. DART
Alan Echt, M.P.H., C.I.H.

The specific aims of this project include: 1) identifying industries where fine Be particle control is an issue; 2) characterization of exposure within these industries, and assessment of applied control methods; 3) evaluation of the limitations of current control methods to reducing fine Be particle exposure; 4) identification of common fine Be particle control issues within industry; and 5) to present information on the current application and effectiveness of control technology to fine Be particles.

9 **Workplace Characterization Study of Dermal Exposure to Beryllium**

Mark Boeniger, Ph.D. DSHEFS
Sally Tinkle, Ph.D. HELD
Mark Hoover, Ph.D. DRDS
Christine Schuler, Ph.D.

This study of dermal exposure to beryllium is supportive of studies being undertaken by DRDS and HELD researchers. The goal is to characterize the skin exposure for job titles with varying degrees of potential skin and inhalation exposures. If the hypothesis is correct that skin exposure is important for worker sensitization to beryllium, workers with low inhalation exposure but high cutaneous beryllium exposure may be sensitized at a rate that is higher than occurs among workers that have low exposure via either route.

10 **Control Technology: Exposure Assessment**

Andrew Maynard, Ph.D. DART

This research project has three key aims: 1) testing and evaluation of commercially available aerosol number concentration and surface area measurement methods, 2) development of new instruments, based on the shortcomings of existing devices, and 3) development of inexpensive, compact, simple-to-operate instrumentation designed for routine aerosol exposure monitoring. Both particle counting and aerosol surface area measurement methods are being investigated with an emphasis on surface area measurements given that toxicology data indicate this to be a key factor. The end products will be a range of well-characterized measurement methods that are suitable for either detailed aerosol characterization (as will be necessary in toxicology, and possibly epidemiology studies), or personal workplace exposure monitoring.

11 **Control Technology: Filtration and Ventilation Systems**

Scott Earnest, Ph.D. DART

This project focuses on whether filtration and ventilation control systems adequately control sub-micrometer particle number and surface area, and if they do not, what are the limitations, and how can these be overcome. Four specific issues are of immediate concern: 1) investigating sub-

micrometer particle re-entrainment and re-circulation within industrial air re-circulation systems, 2) investigating the mechanisms leading to nanoparticle filter penetration, and development of effective filtration technologies, 3) investigating sub-micrometer particle break-through in aged electrostatic filters, and 4) characterizing high efficiency filter performance during bimodal aerosol loading.

12 Lung Cancer Case-Control Study

Wayne Sanderson, Ph.D. DSHEFS
Elizabeth Ward, Ph.D.
Martin Petersen, Ph.D.
Kyle Steenland, Ph.D.

Cohort mortality studies have found elevated lung cancer mortality among beryllium-exposed workers, but none evaluated the association between beryllium exposure level and lung cancer risk. A nested case-control study of lung cancer within a beryllium processing plant was conducted to investigate the relationship between level of beryllium exposure and lung cancer. Lung cancer cases were identified by mortality follow-up through 1992 of a cohort of male workers at a beryllium alloy production plant. This study is complete and manuscripts presenting the results of this study were published in 2001 in the American Journal of Industrial Medicine.

13 Interventions to Control Take-Home Beryllium Exposures of Machine Shop Workers

Wayne Sanderson, Ph.D. DSHEFS
Lauralynn Taylor, M.S.P.H.
Paul Henneberger, Sc.D. DRDS

During an industrial hygiene survey to evaluate airborne beryllium exposures inside the plant, a cross-sectional survey measuring beryllium contamination on workers' hands and inside their personal vehicles was conducted by NIOSH to evaluate the potential take-home beryllium exposures. Many workers did not change out of their work clothes and shoes at the end of their work shift increasing the risk of taking beryllium home to their families. Wipe samples collected from workers' hands and vehicle surfaces revealed that many workers both carried residual beryllium on their hands and contaminated the inside of their vehicles when leaving work. A safe level of beryllium contamination on surfaces is not known, but it is prudent to reduce the potential for workers to carry beryllium away from the worksite.

Appendix 2: Listing of NIOSH Beryllium Publications

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Stefaniak AB, Hoover MD, Dickerson RM, Peterson EJ, Day GA, Breysse PN, Kent MS, and Scripsick RC. Surface Area of Respirable Beryllium Metal, Oxide, and Copper Alloy Aerosols and Implications for Assessment of Exposure Risk of Chronic Beryllium Disease, *Am Ind Hyg Assoc J*. (in press)

McCanlies, E.C. and Weston, A.: Immunogenetic Factors in Berylliosis. *Human Genetic Epidemiology* (in press).

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Ward E, Okun A, Ruder A, Fingerhut M, and Steenland K. A Mortality Study of Workers at Seven Beryllium Processing Plants. *Am J Ind Med* 1992; 22:885-904.

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Steenland K and Ward E, Lung cancer incidence among patients with beryllium disease: a cohort mortality study. *J Natl Cancer Inst*. 1991; 83:1380-1385.