Free Executive Summary

Managing Health Effects of Beryllium Exposure

Committee on Beryllium Alloy Exposures, Committee on Toxicology, National Research Council

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Committee on Beryllium Alloy Exposures

Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Beryllium is a lightweight metal that is used for its exceptional strength and high heat-absorbing capability. Beryllium and its alloys can be found in many important technologies in the defense and aeronautics industries, such as nuclear devices, satellite systems, radar systems, and aircraft bushings and bearings.

Pulmonary disease associated with exposure to beryllium has been recognized and studied since the early 1940s, and an occupational guideline for limiting exposure to beryllium has been in place since 1949. Over the last few decades, much has been learned about chronic beryllium disease and factors that contribute to its occurrence in exposed people. Despite reduced workplace exposure, chronic beryllium disease continues to occur. In addition, beryllium has been classified as a likely human carcinogen by several agencies, such as the International Agency for Research on Cancer, the National Toxicology Program, and the U.S. Environmental Protection Agency. Those developments have led to debates about the adequacy of the long-standing occupational exposure limit for protecting worker health. To help to determine the steps necessary to protect its workforce from the effects of beryllium used in military aerospace applications, the U.S. Air Force asked the Committee on Toxicology of the National Research Council to conduct an independent review of the scientific literature on beryllium and to estimate chronic inhalation exposure levels that are unlikely to produce adverse health effects in military personnel and civilian contractors.

In response to the Air Force's request, the National Research Council convened the Committee on Beryllium Alloy Exposures, which prepared this report. The members of the committee were selected for their expertise in pulmonary and occupational medicine, epidemiology, industrial hygiene, inhalation toxicology, immunotoxicology, pathology, biostatistics, and risk assessment (see Appendix A for biographic information on the members).

To help the committee in its review, two data-gathering meetings were held in early 2007. The committee is grateful to the people who gave presentations on their research in and experience with beryllium exposure and disease. They include John Balmes (University of California, San Francisco), David DeCamp (Air Force Institute of Operational Health), Terry Gordon (New York University School of Medicine), Kathleen Kreiss (National Institute for Occupational Safety and Health), David Louis (Air Force Materiel Command), Lisa Maier (National Jewish Medical and Research Center), Aleksandr Stefaniak (National Institute for Occupational Safety and Health), and Paul Wambach (U.S. Department of Energy).

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of the independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following for their review of this report: John Balmes, University of California at San Francisco; Marc Kolanz, Brush Wellman, Inc.; Kathleen Kreiss, National Institute for Occupational Safety and Health; Michael Luster, consultant; Lisa Maier, National Jewish Medical and Research Center; David Michaels, the George Washington University; Martha Sandy, California Environmental Protection Agency; and Timothy Takaro, Simon Fraser University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by Frank Speizer, Harvard School of Public Health. Appointed by the National Research Council, he was responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the authoring committee and the institution.

The committee is grateful for the assistance of National Research Council staff in preparing the report. It particularly wishes to acknowledge the support of Project Director Susan Martel, who coordinated the project and contributed to the committee's report. Other staff members who contributed to this effort are James Reisa, director of the Board on Environmental Studies and Toxicology; Patrick Baur, research assistant; Tamara Dawson, program associate; Norman Grossblatt, senior editor; and Mirsada Karalic-Loncarevic, manager of the Technical Information Center.

Finally, I thank all the members of the committee for their efforts throughout the development of this report.

Charles H. Hobbs, DVM
Chair, Committee on Beryllium Alloy Exposures

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AEC	Atomic Energy Commission
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	bronchoalveolar lavage
BeLPT	beryllium lymphocyte proliferation test
BeS	beryllium sensitization
CBD	chronic beryllium disease
CI	confidence interval
COT	Committee on Toxicology
DLCO	carbon monoxide diffusing capacity
DLCO/VA	carbon monoxide diffusing capacity per liter of alveolar volume
DOE	U.S. Department of Energy
EPA	U.S. Environmental Protection Agency
HLA	human leukocyte antigen
HRCT	high-resolution computed tomography
IARC	International Agency for Research on Cancer
LANL	Los Alamos National Laboratory
LOAEL	lowest-observed-adverse-effect level
MHC	major histocompatibility complex
MIF	migration-inhibitory factor
MMAD	mass median aerodynamic diameter
MOUDI	micro-orifice uniform deposition impactor
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PPE	personal protective equipment
PPV	positive predictive value
RfD	reference dose
SMR	standardized mortality ratio
SSA	specific surface area
SUF	serum ultrafiltrate
TGF	transforming growth factor
TLV	Threshold Limit Value
TRI	Toxic Release Inventory
TWA	time-weighted average
VD/VT	ratio of dead space to tidal volume

Managing Health Effects of Beryllium Exposure

Summary

Beryllium is an important metal that is used in a number of industries—including the defense, aerospace, automotive, medical, and electronics industries—because of its exceptional strength, stability, and heat-absorbing capability. It is found in a variety of technologies, including nuclear devices, satellite systems, missile systems, radar systems, bushings and bearings in aircraft and heavy machinery, x-ray machines used for mammography, cellular-telephone components, computer components, and connectors for fiber optics.

Since the early 1940s, beryllium has been recognized as posing an occupational hazard in manufacturing and production settings. Workers in the 1940s exposed to high concentrations of beryllium were reported to develop acute beryllium disease, an acutely toxic, pneumonitis-like lung condition. Cases of acute beryllium disease have been rarely reported in recent decades as respiratory exposure to beryllium has become better controlled in the workplace. Beryllium can also induce a condition known as chronic beryllium disease (CBD), a disease primarily affecting the lungs that is caused by a specific immune response to beryllium. An 8-h occupational guideline for limiting exposure to beryllium to 2 $\mu g/m^3$ has been in place since 1949. That guideline was successful in practically eliminating acute beryllium disease, but the risk of CBD persists.

To help determine the steps necessary to protect its workforce from the adverse effects of exposure to beryllium used in military aerospace applications, the U.S. Air Force requested that the National Research Council conduct an independent evaluation of the scientific literature on beryllium, and make judgments about potential health risks. The request specified that two reports be produced to accomplish those tasks (see Box S-1). The first report, issued in 2007, provided a review of the scientific literature on beryllium. That review is expanded in this, the second report, in which the committee also considers the maximum chronic inhalation exposure to beryllium that is unlikely to produce adverse health effects, discusses carcinogenic risks, and describes testing methods for surveillance and monitoring of worker populations.

The primary health effects of interest in connection with beryllium are beryllium sensitization (BeS), CBD, and lung cancer. After critically reviewing the available literature on those outcomes, the committee concluded that available scientific information does not enable the identification of an inhalation exposure that is unlikely to lead to BeS or CBD. The best approach for protecting the Air Force's workforce from the effects of beryllium exposure is to establish a beryllium exposure- and disease-management program. The program should be designed to reduce exposure to beryllium to the lowest feasible level and should include a medical-surveillance program for identifying and following affected workers. The committee also found that uncertainties in the epidemiologic evidence limit the ability to derive quantitative carcinogenic risk estimates associated with current magnitudes of beryllium exposure. How the committee came to those conclusions and recommendations is elaborated below.

BERYLLIUM SENSITIZATION AND CHRONIC BERYLLIUM DISEASE

It is well established that beryllium can cause sensitization and CBD. BeS is an immune response triggered by beryllium exposure in susceptible people. It is not a disease, but it is a predictor of CBD in

BOX S-1 Statement of Task of the Committee on Beryllium Alloy Exposures

In its first report, the committee will provide an independent review of the toxicologic, epidemiologic, and other relevant data on beryllium. It will review both carcinogenic and noncarcinogenic effects. In its second report, the committee will estimate chronic inhalation exposure levels for military personnel and civilian contractor workers that are unlikely to produce adverse health effects. The committee will provide carcinogenic risk estimates for various inhalation exposure levels. It will consider genetic susceptibility among worker subpopulations. If sufficient data are available, the committee will evaluate whether beryllium-alloy exposure levels should be different from those of other forms of beryllium because of differences in particle size. The committee will identify specific tests for worker surveillance and biomonitoring. It will also comment on the utility of the beryllium lymphocyte proliferation test (BeLPT). Specifically, the committee will determine the value of the borderline or a true positive test in predicting CBD, its utility in worker surveillance, further followup tests needed for workers with positive BeLPT results (such as thin-slice computed-tomography bronchoscopy and biopsy), the likelihood of developing CBD after a true positive test, and a standardized method for achieving consistent test results in different laboratories. The committee will consider whether there are more suitable tests that would be more accurate as screening or surveillance tools. The committee will also identify data gaps relevant to risk assessment of beryllium alloys and make recommendations for further research.

workers with known exposure to beryllium. CBD is a systemic granulomatous disorder that affects mainly the lungs. CBD has a clinical spectrum that can range from asymptomatic disease with no deficits in lung function or radiographic abnormalities to end-stage lung disease. Asymptomatic cases are usually identified when workers in a beryllium-surveillance program test positive for BeS and followup medical evaluations reveal lung granulomas or other evidence of disease. Only a fraction of people who are exposed to beryllium become sensitized, and only some of those who are sensitized develop CBD. A number of factors appear to influence susceptibility to sensitization and development of CBD, including magnitude of exposure, physicochemical properties of beryllium, route of exposure, and host factors.

The committee was asked to consider the toxicity of different forms of beryllium because the Air Force uses beryllium alloys in its aerospace applications and the exposure scenarios probably differ from settings in which beryllium is mined, manufactured, or processed. The committee found that the physicochemical properties of the different forms of beryllium may affect their deposition in lungs and their bioavailability and may be important factors in the development and course of CBD. However, there are insufficient data from the epidemiologic and toxicologic literature to draw firm conclusions about the relative chronic toxicity of different forms. Thus, the committee considered risks posed by beryllium exposure broadly to include all forms of beryllium.

The immunopathogenic mechanisms underlying BeS and progression to CBD have been investigated largely through clinical studies and experiments focused on the human immune system. Attempts to develop animal models of CBD have had little success. Acute toxicity may be somewhat similar in animals and humans, but immunologic mechanisms underlying BeS and progression to CBD are not well represented by animal models. For example, the beryllium-induced immunologic disease in laboratory animals appears to regress when exposure is stopped, whereas in humans it persists or progresses. Thus, it is not possible to rely on animal models to determine potential human health effects of low-dose chronic beryllium exposures in workers.

It is clear from animal and human data that susceptibility to BeS and CBD has genetic components. Attempts to identify the genetic components of susceptibility have centered mainly on investigating polymorphisms of the major histocompatibility complex class II and proinflammatory genes. Alleles of the HLA-DP gene containing glutamic acid at the 69th position of the β chain (HLA-DPβGlu69) appear to be the most important markers of susceptibility to CBD. However, the presence of that marker alone does not necessarily confer susceptibility, nor is its absence a guarantee of nonsusceptibility. In addition to exposure, T-cell receptor expression, inflammation-related genes, and

other potential modifier genes may play roles in sensitization and disease progression. Efforts are under way to create humanized mouse models with specific human alleles associated with a range of BeS and CBD risk.

Epidemiologic studies have shown that detection of BeS and CBD occurs in settings where airborne exposure to beryllium is below the current occupational standard of 2 $\mu g/m^3$, but they have not given a clear indication of how much lower the standard would have to be set to be fully protective. It has also been hypothesized that skin exposure to beryllium may contribute to BeS and CBD. Thus, the committee concludes that the available data are insufficient for estimating an inhalation exposure magnitude that will prevent BeS and CBD in settings where beryllium has the potential for being aerosolized. Beryllium industries have succeeded in reducing the prevalence of BeS and CBD by establishing exposure- and disease-management programs to minimize exposure and to monitor workers for adverse health effects.

Recommendation: In the absence of sufficient evidence to establish a chronic inhalation level for beryllium that that is unlikely to result in BeS or CBD, the committee recommends that the Air Force implement an exposure- and disease-management program to protect its workers. The program should involve industrial-hygiene assessments to identify potentially exposed workers, to eliminate as many job tasks involving exposure to beryllium particles as possible, and to minimize the number of workers performing those tasks; screening of potentially exposed workers for BeS; medical management of BeS and CBD; and stringent engineering and work-practice controls to keep beryllium exposure as low as is feasible. Important aspects of the recommended exposure- and disease-management program are shown in Figure S-1. The program should evolve as more is learned about exposure and disease prevalence in the Air Force.

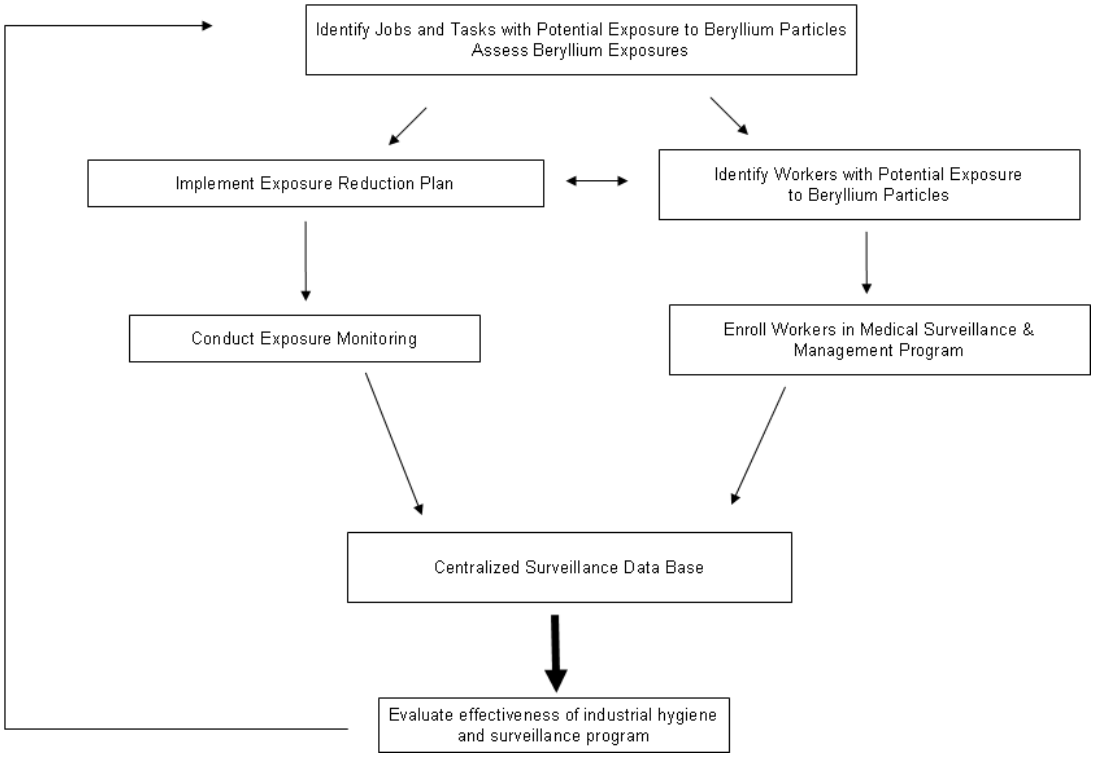

FIGURE S-1 Beryllium exposure and disease management program.

BERYLLIUM LYMPHOCYTE PROLIFERATION TEST

The beryllium lymphocyte proliferation test (BeLPT) is an in vitro test of BeS that will be integral to any beryllium-related screening program. No alternative tests of sensitization or biomarkers of exposure have been adequately validated to be put into practice outside research settings.

In the BeLPT, mononuclear cells derived from peripheral blood or bronchoalveolar-lavage (BAL) fluid are challenged with beryllium salts in vitro. A response is considered positive if beryllium induces proliferation of sensitized lymphocytes. The test is used both for diagnostic evaluation of patients who present with possible CBD and for medical surveillance of workers. For example, the BeLPT is a tool that can help to differentiate CBD from other interstitial granulomatous lung diseases, such as sarcoidosis and chronic hypersensitivity pneumonitis. When the test is used to identify at-risk populations, rather than as an individual screening or diagnostic test, it is useful for identifying facilities, areas in a given facility, and job tasks that have risk for CBD. Screening of healthy exposed workers with the BeLPT has also enabled the detection of BeS in such workers and has enabled earlier diagnosis of CBD. Despite some issues regarding the reproducibility, sensitivity, and specificity of the BeLPT, the committee judged it to be an adequate assay for use in a surveillance program.

The committee was asked by the Air Force to comment on five questions about the BeLPT. The questions and the committee's answers are presented below.

- **What is the value of a borderline or true-positive BeLPT result in predicting CBD?** A borderline test result in combination with a positive test result is generally considered indicative of sensitization. If a borderline result is not preceded or followed by a positive result, the tested person is considered nonsensitized. The committee considers a true-positive (or confirmed abnormal) blood BeLPT result to be a predictor of CBD in a worker with known exposure to beryllium, but there are insufficient data for accurate prediction of risk of progression.

- **What is the utility of the BeLPT in worker surveillance?** The BeLPT identifies BeS in exposed workers. When used to identify at-risk populations, rather than as a screening or diagnostic test, the BeLPT has been shown to be useful for identifying facilities or jobs that pose risk. Medical surveillance with the BeLPT has been able to detect risk of CBD better than traditional air sampling because BeS can occur at low air concentrations and possibly from skin exposure. The committee stresses, however, that BeLPT screening should not be used as the first line of defense against exposure.

- **What followup tests should be performed on workers with positive BeLPT results?** Workers with positive BeLPT results should undergo further medical evaluation, which should generally include a medical and occupational questionnaire, pulmonary-function tests that include lung volumes and carbon monoxide diffusing capacity, and high-resolution computed tomography of the chest when indicated. After review of the test results, consideration should be given to performing bronchoscopy with BAL, transbronchial biopsy, and possibly other tests. In the clinical setting, the decision to perform those examinations is made case by case.

- **What is the likelihood of developing CBD after a true-positive test result?** Some studies have reported that CBD is diagnosed in up to 50% or more of screened workers who have true-positive BeLPT results, and the conversion rate from BeS to CBD has been estimated to be 6-8% per year. However, the estimated conversion rate was based on a single cohort of workers. Although those with positive BeLPT results are at an increased risk for CBD, the available evidence is insufficient to make quantitative predictions about the magnitude of the risk.

- **Is there a standardized method for achieving consistent test results in different laboratories?** No standardized method is used in laboratories in the United States. Preliminary results of

a study in Canada showed that concordance in results between laboratories improved when testing procedures were closely matched (e.g., when such variables as dose, times, and controls were standardized). Concordance in laboratory testing and analysis and a standardized testing algorithm should reduce variation between laboratories but will not address issues regarding the sensitivity and specificity of the test.

CANCER

There is evidence from inhalation-exposure studies that beryllium can cause lung cancer in laboratory animals. Epidemiologic studies have reported increases in lung-cancer risk in two worker cohorts exposed to beryllium. Those studies were instrumental in forming the basis of the current cancer classifications of the International Agency for Research on Cancer, the U.S. Environmental Protection Agency, and the National Toxicology Program. New studies and reanalyses of data performed since those assessments have not added substantially to understanding of the carcinogenicity of beryllium or of the dose-response relationship between beryllium exposure and lung cancer. The committee agrees with the other agencies that the balance of the evidence supports a conclusion that beryllium is likely a human carcinogen.

The committee was asked to develop carcinogenic risk estimates for different magnitudes of inhalation exposure to beryllium; however, the committee judged that the available human and animal data are inadequate to support a dose-response analysis with low-dose extrapolation to current exposure magnitudes. A useful cancer dose-response assessment cannot be conducted until more information is available on existing or new worker cohorts regarding complete work history, possible exposure to other carcinogens, and exposure history. Furthermore, carcinogenic risk estimates would be of limited utility in light of the committee's recommendation that the Air Force implement an exposure- and disease-management program to reduce exposure to beryllium to the lowest feasible magnitude to prevent BeS and CBD.

1

Introduction

Beryllium is a low-density metal that is used in various applications in a number of industries—including the automotive, aerospace, defense, medical, and electronics industries—because it is exceptionally strong, is light in weight compared with other metals, has high heat-absorbing capability, and has dimensional stability in a wide range of temperatures. The three forms of beryllium-containing materials used in manufacturing processes are beryllium alloys, metallic beryllium, and beryllium oxide. Beryllium alloys are made primarily with copper, nickel, or aluminum. The amount of beryllium in alloys depends on the desired strength and electric conductivity of the product. Beryllium-copper alloys are the most commonly used and are found in electric connectors and relays, bushings and bearings in aircraft and heavy machinery, submarine cable housing and pivots, switches in automobiles, telecommunication equipment, computers, home appliances, cellular phones, and connectors for fiber optics (Kolanz 2001; ATSDR 2002). The aeronautics and defense industries use alloys that have a high beryllium content (40-100%) to make electro-optical targeting and infrared countermeasure devices, missile systems, and radar systems (Kolanz 2001). Beryllium metal is used in aircraft disk-brake systems, fusion reactors, nuclear devices, satellite systems, missile-guidance systems, navigational systems, heat shields, high-speed computer and audio components, and x-ray machines for mammography. Applications of beryllium oxide include high-technology ceramics, electric insulators, rocket nozzles, crucibles, laser structural components, automotive ignition systems, and radar electronic countermeasure systems (Kolanz 2001; ATSDR 2002; Kreiss et al. 2007).

HISTORICAL REVIEW OF OCCUPATIONAL EXPOSURE LIMITS

It has long been recognized that exposure to beryllium in occupational settings poses health hazards, primarily in the forms of acute beryllium disease and chronic beryllium disease (CBD). In 1949, the U.S. Atomic Energy Commission (now the U.S. Department of Energy [DOE]) recommended the first occupational exposure limit (OEL) for beryllium, 2.0 $\mu g/m^3$. That limit was adopted by the American Conference of Governmental Industrial Hygienists (ACGIH), the National Institute for Occupational Safety and Health, the Occupational Safety and Health Administration (OSHA), the American Industrial Hygiene Association, and the American National Standards Institute (see Table 1-1). The OEL of 2.0 $\mu g/m^3$ still stands although it has been challenged on several occasions.

The basis of the original standard was an estimate of the toxicity of beryllium in relation to other metals. It was assumed that beryllium toxicity was comparable with that of heavy metals on an atom-for-atom basis. Mercury and lead had occupational exposure limits of around 100 $\mu g/m^3$, and that value was divided by 20 because the atomic weight of beryllium is about one-twentieth that of mercury and lead. The resulting value was divided by 2.5 to provide a margin of safety because understanding of CBD was lacking. The adequacy of the OEL of 2.0 $\mu g/m^3$ was evaluated periodically in the 1960s; each time, it was deemed adequate because acute beryllium disease had become a rare occurrence and the incidence of CBD had become much lower.

TABLE 1-1 Selected Exposure Guidelines and Actions Taken on Beryllium

Agency	Year	Guideline or Action	Notes and References
DOE	1949	OEL, 2 μg/m^3 (DWA)	DWA averaged from samples over quarterly periods
	1999	8-h TWA action level, 0.2 μg/m^3	Action level triggers worker-protection measures; issued while OSHA was completing rule-making (64 Fed. Reg. 68854 [1999]).
	1999	Surface contamination standard, 0.3 μg/100 cm^2	Triggers worker-protection measures, including protective clothing and equipment (10 CFR 850.29-30 [1999])
	1999	Surface contamination standard (for release to the general public or for use in a non-beryllium area), 0.2 μg/100 cm^2	10 CFR 850.31 (1999)
	2006	Worker safety and health program	71 Fed. Reg. 6858 (2006)
ACGIH	1959	TLV, 2 μg/m^3 (8-h TWA)	ACGIH 2006
	1975	A2 carcinogen (suspected human carcinogen)	ACGIH 2006
	1997	A1 carcinogen (confirmed human carcinogen)	ACGIH 2006
	1999	TLV, 0.2 μg/m^3 (8-h TWA, inhalable particulate mass, sensitizer; *notice to change*)	ACGIH 2006
	2005	TLV, 0.05 μg/m^3 (8-h TWA, inhalable particulate mass, sensitizer, skin exposure; *notice of intended change*)	ACGIH 2006
NIOSH	1972	REL, 2 μg/m^3 (8-h TWA)	NIOSH 1972
	1977	REL, 0.5 μg/m^3 (10-h TWA)	Potential occupational carcinogen; NIOSH recommended that OSHA reduce PEL (NIOSH 1977); not clear from documentation whether REL in 1977 was for 8 h or 10 h NIOSH (2005) reports it as 10-h TWA
OSHA	1971	PEL, 2 μg/m^3 (8-h TWA)	PEL adopted from ANSI standard (67 Fed. Reg. 70700 [2002])
	1975	PEL, 1 μg/m^3 (8-h TWA; *proposed value*)	Proposed value based on presumption of carcinogenicity; never promulgated (40 Fed. Reg. 48814 [1975]; 67 Fed. Reg. 70700 [2002])
	1999, 2001	OSHA petitioned to issue emergency temporary standard	Petition denied by OSHA, but OSHA stated intent to begin data-gathering (67 Fed. Reg. 70700 [2002])
	2002	Request for information issued	67 Fed. Reg. 70700 (2002)
AIHA	1964	Hygienic standard, 2 μg/m^3 (8-h TWA)	Trucano 1964
ANSI	1970	OEL for particles ≤5 μm, 2 μg/m^3 (8-h TWA)	ANSI 1970

(Continued)

TABLE 1-1 Continued

Agency	Year	Guideline or Action	Notes and References
IARC	1993	Group 1 human carcinogen	IARC 1993
EPA	1998	RfC, 0.02 $\mu g/m^3$	Value based on sensitization and progression to CBD (EPA 1998a)
		RfD, 0.002 mg/kg-day	Value based on intestinal lesions in dogs (EPA 1998a)
		Air unit risk = 2.4×10^{-3} per $\mu g/m^3$	Value based on lung cancer (EPA 1998a)
		24-h ambient-air limit (averaged over 30 d), = 0.01 $\mu g/m^3$	40 CFR Sec. 61.32
Cal/OSHA	2006	PEL, 0.2 $\mu g/m^3$	California Labor Code, § 144.6, Title 8, § 5155

ABBREVIATIONS: ACGIH, American Conference of Governmental Industrial Hygienists; AIHA, American Industrial Hygiene Association; ANSI, American National Standards Institute; Cal/OSHA, California Occupational Safety and Health Administration; CBD, chronic beryllium disease; DOE, U.S. Department of Energy; DWA, daily weighted average; EPA, U.S. Environmental Protection Agency; IARC, International Agency for Research on Cancer; NIOSH, National Institute for Occupational Safety and Health; OEL, occupational exposure limit; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; RfC, reference concentration (inhalation); RfD, reference dose (oral); TLV, Threshold Limit Value; TWA, time-weighted average.

Current scientific questions about exposure to beryllium in the workplace are related to CBD and cancer. Over the last 40 years, much has been learned about how beryllium causes CBD, and the diagnostic criteria for the disease have changed. Advances in medical and diagnostic technology allow physicians to identify beryllium-exposed workers with evidence of sensitization or milder forms of CBD (see Chapter 3). Research into dose-response relationships indicates that particle size, chemical form, concentration, and genetic factors may all play roles in determining whether a person develops CBD.

In addition, there has been debate over beryllium's carcinogenic potential. In 1975, OSHA proposed to lower its permissible exposure limit to 1 $\mu g/m^3$ on the presumption that beryllium was a carcinogen. However, that revision was never promulgated. OSHA was petitioned in 1999 and 2001 to issue an emergency temporary standard. The petitions were denied, but the agency indicated that it would begin data-gathering to revisit the adequacy of the standard for protecting worker health. The agency issued a formal request for information in 2002 (67 Fed. Reg. 70700 [2002]). Peer review of OSHA's health-effects and risk-assessment report is expected to be completed by November 2008 (73 Fed. Reg. 24723 [2008]).

Other agencies have taken action in re-evaluating their occupational exposure guidelines for beryllium. In 1999, DOE established an action level of 0.2 $\mu g/m^3$ intended to trigger workplace precautions and control measures to protect workers at DOE facilities (64 Fed. Reg. 68854 [1999]). That action level is applicable only to DOE and DOE-contractor facilities and was established because DOE considered the OEL of 2 $\mu g/m^3$ to be inadequate to protect worker health. DOE also established two surface-contamination guidelines for beryllium to reduce its accumulation on surfaces and its spread outside specific work areas (10 CFR 850.29-30 [1999]). A beryllium surface guideline was set at 3 $\mu g/100\ cm^2$ for operational areas where workers may be exposed to beryllium. The second guideline for the surfaces of equipment and other items to be released to the general public or for use in DOE nonberyllium work areas was set at 0.2 $\mu g/100\ cm^2$. No guidelines were set for skin exposure. In 2005, ACGIH proposed revision to its Threshold Limit Value for beryllium, but it has not yet issued a final determination.

OTHER EXPOSURE GUIDELINES

Exposure guidelines for beryllium designed for the general public have been established by the U.S. Environmental Protection Agency (EPA 1998a). For inhalation exposures, EPA has the reference concentration (RfC), which is defined as an estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a continuous inhalation exposure of the human population (including susceptible subpopulations) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. For beryllium, the principal health end point selected to derive the RfC was beryllium sensitization progressing to CBD. Observations in an occupational-exposure study (Kreiss et al. 1996) and a community-exposure study (Eisenbud et al. 1949) supported a lowest observed-adverse-effect level (LOAEL) of 0.20 $\mu g/m^3$. That value was adjusted by applying two uncertainty factors of 3 to account for the poor quality of the exposure assessments in those and supporting epidemiologic studies and to account for use of an LOAEL instead of a no-observed-adverse-effect level. The adjustment resulted in an RfC of 0.02 $\mu g/m^3$.

EPA (1998a,b) also classifies beryllium as a likely human carcinogen. For carcinogens, EPA calculates an inhalation unit risk, which is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$. For beryllium, the unit risk is estimated to be 2.4×10^{-3}. On the basis of that value, EPA estimated that air concentrations of 0.04, 0.004, and 0.0004 $\mu g/m^3$ would result in cancer risks of 1×10^{-4}, 1×10^{-5}, and 1×10^{-6}, respectively. EPA is updating its human health risk assessment of beryllium.

COMMITTEE'S TASKS

To determine the steps necessary to protect its workforce from the adverse effects of exposure to beryllium used in military aerospace applications, the U.S. Air Force requested an independent evaluation of the health risk posed by beryllium. An ad hoc committee under the oversight of the National Research Council's standing Committee on Toxicology was tasked with writing two reports to address the request. For the first report, which was issued in 2007, the committee was asked to provide an independent review of the toxicologic, epidemiologic, and other relevant data on beryllium (NRC 2007). For this, its second report, the committee was asked to estimate levels of chronic inhalation exposure of military personnel and civilian contractor workers that are unlikely to produce adverse health effects. The committee was asked to provide estimates of carcinogenic risk posed by various levels of inhalation exposure. Genetic susceptibility among worker subpopulations was to be considered. If sufficient data were available, the committee was to evaluate whether levels of beryllium-alloy exposure should be different from those of exposure to other forms of beryllium because of differences in particle size. The committee was asked to identify specific tests for worker surveillance and biomonitoring and to comment on the utility of the beryllium lymphocyte proliferation test (BeLPT). Specifically, the committee was asked to determine the value of the borderline or a true-positive test in predicting CBD, its utility in worker surveillance, further followup tests needed for workers with positive BeLPT results (such as thin-slice high-resolution computed tomography, bronchoscopy, and biopsy), the likelihood of developing CBD after a true-positive test, and a standardized method of achieving consistent test results in different laboratories. Consideration was to be given to whether there are more suitable tests that would be more accurate as screening or surveillance tools. The committee was also asked to identify data gaps relevant to risk assessment of beryllium alloys and to make recommendations for further research.

COMMITTEE'S APPROACH

To accomplish its tasks, the committee held four meetings from February 2007 to February 2008. The meetings included data-gathering sessions that were open to the public. The committee heard presentations from the U.S. Air Force and from researchers in government and academe who were involved in beryllium research (see Preface for list of speakers). The committee also reviewed a large body of scientific literature on beryllium. The primary health concerns related to beryllium—sensitization, CBD, and lung cancer—make up the bulk of the literature. A much smaller database was found on other toxicity end points, such as reproductive and developmental effects. The committee's first report (NRC 2007) provided a survey of the literature on beryllium that was available at the end of April 2007. The purpose was to identify topics on which to focus a more critical review. In the present report, the literature review has been revised and updated, and the committee draws conclusions about the potential health risks posed by beryllium exposure and makes recommendations for an exposure-management and disease-management program.

ORGANIZATION OF THE REPORT

The remainder of this report is organized in six chapters. Chapter 2 reviews exposure factors important for assessing health risks associated with beryllium. It includes a review of the exposure assumptions that underlie existing exposure standards, consideration of exposures in natural and anthropogenic settings, and an examination of how physiochemical characteristics and particle sizes are associated with risk of disease. Chapter 3 provides an overview of the epidemiologic and clinical literature on beryllium sensitization and CBD. Chapter 4 presents information mainly from animal studies on the pathogenesis and mode of action of CBD and information on genetic susceptibility. Chapter 5 focuses on the evidence of beryllium's carcinogenic potential and considers carcinogenic risk estimates.

Other health end points, such as reproductive and developmental effects, are reviewed in Chapter 6. Finally, Chapter 7 discusses the design of a beryllium exposure- and disease-management program for workers in the Air Force.

2

Exposure Assessment

The committee has reviewed the literature describing exposure to beryllium to provide a basis for examining questions relevant to the identification of exposure-response relationships and the development of health-protection standards. Worker-protection standards are the focus of this effort, but an understanding of natural background exposures and anthropogenic exposures in various settings provides a useful context for understanding occupational exposures that lead to disease. Consequently, those exposures are briefly discussed here. The committee conducted its literature review in recognition that appropriate standards may vary with health end point. Exposures that lead to the principal end points of concern in connection with beryllium—beryllium sensitization (BeS), chronic beryllium disease (CBD), and cancer—are likely to have distinct physicochemical and dose-response characteristics.

The committee formulated the following specific questions to guide its literature review:

- What are the current and potential future uses and sources of beryllium?
- What are the nature and magnitude of and variation in natural and anthropogenic background exposure via diet, drinking water, soil contact, and inhalation?
- What are the nature and magnitude of and variation in occupational exposure to beryllium, and how have changes in workplace practices changed beryllium exposure?
- Have changes in workplace practices and exposures affected the ability to identify exposure-response relationships?
- What sampling and analytic methods have been used, and how have changes in them affected exposure estimates?
- What exposure metrics should be used to evaluate air and surface contamination or skin exposure? Will the metrics for sensitization and CBD differ from those for cancer risk?

We first describe beryllium sources and uses and then briefly review beryllium toxicokinetics. Exposure data on naturally occurring, background, and occupational exposure to beryllium are described next, and later sections examine sampling and analytic methods and exposure metrics for air and surface contamination and skin exposure.

SOURCES AND USES

This section reviews forms and characteristics of beryllium that are present in natural and anthropogenic settings. Beryllium metal, with atomic number 4, belongs to group IIA of the periodic table (alkaline-earth elements) and is chemically similar to aluminum; it has a high charge-to-nucleus ratio that leads to amphoteric behavior and a strong tendency to hydrolyze (EPA 1998b; ATSDR 2002). It has many unique chemical properties, being less dense than aluminum and stiffer than steel (EPA 1998b). Because of its small atomic size, its most stable compounds are formed with small anions, such as fluoride and oxide. Beryllium is also capable of forming strong covalent bonds and may form organometallics, such as dimethyl beryllium [$Be(CH_3)_2$] (EPA 1998b).

Beryllium has been estimated to be present in the earth's crust at 2-5 mg/kg, and soil concentrations in the United States were reported to average 0.63 mg/kg and to range from less than 1 to 15 mg/kg (ATSDR 2002). In its review of beryllium, the Agency for Toxic Substances and Disease Registry (ATSDR 2002) reported that surveys had detected beryllium in less than 10% of samples of U.S. surface water and springs, but detection limits are not reported in the review. The low concentrations in water probably reflect beryllium's typically entering water as beryllium oxide, which slowly hydrolyzes to the insoluble compound beryllium hydroxide (EPA 1998b).

Beryllium concentrations in U.S. air have typically been lower than the detection limit of 0.03 ng/m^3 (ATSDR 2002). Natural sources of airborne beryllium are windblown dust and volcanic particles, which are estimated to contribute 5 and 0.2 metric tons per year, respectively, to the atmosphere (Table 2-1). The principal anthropogenic contributor to airborne emission is coal combustion. World coals have been reported to have a wide range of beryllium concentrations, from 0.1 to 1,000 mg/kg (Fishbein 1981), and the range in U.S. coal is 1.8-2.2 mg/kg (ATSDR 2002). On the basis of coal combustion of 640 million metric tons per year and a beryllium emission factor of 0.28 g/ton, the U.S. Environmental Protection Agency (EPA 1998b) has estimated that as much as 180 metric tons of beryllium may be emitted each year from U.S. coal combustion; fuel oil is burned at the rate of 148 million metric tons per year and has a beryllium emission factor of 0.048 g/ton, which would mean another 7.1 metric tons of beryllium released each year. Those estimates appear to conflict with emission estimates from the Toxic Release Inventory (TRI), which suggest a total of 3.5 tons per year released by electric utilities (Table 2-1); however, the TRI data are noted to be limited to particular types of facilities and to constitute an incomplete list (ATSDR 2002). The U.S. Department of Energy (DOE 1996) reported that beryllium in stack emissions of coal-fired power plants were 100-1,000 times greater than ambient air concentrations.

In 1991, Rossman et al. (1991) reported that 45 beryllium-containing minerals had been identified, including silicates, aluminum silicates, and aluminum oxides. Four were commercially important: beryl, phenakite, bertrandite, and chrysoberyl. Unlike such metals as lead and copper, which have a long history of use, beryllium had no known commercial use until a patent was issued for a beryllium-aluminum alloy in 1918 (Rossman et al. 1991). Production of beryllium-copper alloys began during the 1920s and increased substantially during World War II. Until 1969, beryl ore from pegmatite dikes found widely distributed around the world was the only commercial source of beryllium (Rossman et al. 1991). Since then, a bertrandite deposit in Utah has also been mined. In 1991, world beryllium production was estimated at 3,600 metric tons (Rossman et al. 1991). Releases to the environment from U.S. facilities that produce, process, or use beryllium compounds are tracked in the TRI database. Releases of beryllium to air, water, underground injection, and land are summarized in Table 2-2, and releases of beryllium compounds in Table 2-3. Releases of beryllium are notably high in Ohio because the sole U.S. producer and processor of beryllium (Brush Wellman) is there. Releases of beryllium compounds are more dispersed around the country because many more companies and industries process and use beryllium compounds.

Through the middle of the 20th century, beryllium was used predominantly in fluorescent lamps, nuclear-weapon components, and other defense applications. It is now used in a wide variety of products in various industries (see Table 2-4). As described by Kreiss et al. (2007), those diverse uses may put a growing number of workers at risk for beryllium exposure; however, no systematic surveys designed to detect beryllium exposures in private industry have been conducted. Henneberger et al. (2004) relied on OSHA sampling compliance data to estimate that 26,400-106,000 current workers in private industry other than the primary beryllium industry have potential exposure to beryllium. Those estimates were based on personal 8-h samples collected during OSHA enforcement activities when beryllium concentrations exceeded 1 $\mu g/m^3$. The samples were collected in 1979-1996 and were used to derive percentages of exposed workers in various standard industrial classification codes applied to workforce numbers from 2001. The lower estimate is based on the assumption that only the workers sampled and co-workers with the same job were exposed, whereas the higher estimate assumes that all workers in a job site are exposed. The latter estimate was judged by Henneberger et al. to be a better representation of the potentially exposed population, given reports on development of CBD in minimally exposed workers at

beryllium facilities. They also obtained estimates of currently exposed workers at DOE facilities (8,100), at DOD facilities (18,400), and in the primary beryllium industry (1,500), yielding an overall estimate of 54,400-134,000 U.S. workers having potential exposure to beryllium. Some of the workplaces with detected beryllium concentrations in 1979-1996 may no longer have such exposures, and other workplaces, such as those recycling electronic equipment, may now be sources of exposure. Henneberger et al. (2004) provided a series of recommendations for supplementing their analysis to facilitate more effective identification of and communication with at-risk audiences.

TABLE 2-1 Anthropogenic and Natural Emissions of Beryllium and Beryllium Compounds to the Atmosphere[a]

Emission Source	Emission (tons/year)[b]
Natural	
Windblown dust	5
Volcanic particles	0.2
Anthropogenic[c,d]	
Industry	0.6
Metal mining	0.2
Electric utilities	3.5
Waste and solvent recovery (RCRA)	0.007
Total	9.507

[a]Adapted from Drury et al. 1978; EPA 1987; TRI99 2002.
[b]Units are metric tons.
[c]Data in Toxic Release Inventory are maximum amounts released by each industry. Listing is incomplete because not all types of facilities are included in the estimates.
[d]Sum of fugitive and stack releases is included in releases to air by a given industry.
ABBREVIATION: RCRA, Resource Conservation and Recovery Act.
Source: ATSDR 2002.

TABLE 2-2 Releases of Beryllium Metal to the U.S. Environment from Facilities That Produce, Process, or Use It

		Reported Amounts Released (lb/year)[a]						
State[b]	Number Facilities	Air[c]	Water	Underground Injection	Land	Total On-Site Release[d]	Total Off-Site Release[e]	Total On-Site and Off-Site Release
CA	3	0	No data	No data	No data	0	No data	0
IN	3	0	No data	No data	2,650	2,650	2,415	5,065
LA	1	2	No data	No data	No data	2	No data	2
MO	1	0	No data	No data	10	10	0	10
NC	1	38	No data	No data	No data	38	No data	38
OH	6	721	27	No data	50,352	51,280	9,870	61,150
OK	2	No data	23	No data	5	28	6,830	6,858
PA	1	1	7	No data	No data	8	966	974
SC	1	7	No data	No data	74	81	No data	81
TN	1	No data	No data	No data	No data	No data	No data	No data
UT	1	0	No data	No data	0	0	No data	0
WI	1	No data	No data	No data	No data	No data	No data	No data
Total	22	769	57	0	53,271	54,097	20,081	74,178

[a]Data in Toxic Release Inventory (TRI99 2002) are maximum amounts released by each facility.
[b]Postal Service state abbreviations are used.
[c]Sum of fugitive and stack releases is included in releases to air from given facility.
[d]Sum of all releases to air, water, underground injection wells, and land.
[e]Total amount transferred off site, including to publicly owned treatment works.
Source: ATSDR 2002.

TABLE 2-3 Releases of Beryllium Compounds to the U.S. Environment from Facilities That Produce, Process, or Use Them (TRI99 2002)

		Reported Amounts Released (lb/year)[a]						
State[b]	Number Facilities	Air[c]	Water	Underground Injection	Land	Total On-Site Release[d]	Total Off-Site Release[e]	Total On-Site and Off-Site Release
AL	6	419	250	No data	62,691	63,360	326	63,686
AR	2	197	48	No data	9,130	9,375	1	9,376
AZ	4	50	No data	No data	16,421	16,471	1,630	18,101
FL	3	390	250	No data	5,745	6,385	5	6,390
GA	5	764	0	No data	76,925	77,689	No data	77,689
IL	1	79	850	No data	8,500	9,429	No data	9,429
IN	4	340	63	No data	40,019	40,422	3,808	44,230
KY	5	351	1,221	No data	21,730	29,302	No data	29,302
MD	1	No data	No data	No data	No data	No data	No data	No data
MI	2	313	17	No data	15,000	15,330	250	15,580
MO	3	10	No data	No data	No data	10	555	565
MS	1	2	20	4,100	19	4,141	0	4,141
MT	1	250	No data	No data	6,900	7,150	750	7,900
NC	4	817	403	No data	51,010	52,230	260	52,490
NM	4	112	77	No data	47,724	47,913	39,000	86,913
NY	1	20	0	No data	400	420	No data	420
OH	4	450	30	No data	25,846	26,326	11,422	37,748
PA	4	1,580	16	No data	8,700	10,296	6,411	16,707
TN	2	256	250	No data	14,100	14,606	640	15,246
TX	1	19	0	No data	31,400	31,419	No data	31,419
UT	4	366	No data	No data	299,952	300,318	5	300,323
WI	1	10	5	No data	No data	15	255	270
WV	9	861	10	No data	70,765	71,636	6,800	78,436
WY	1	160	No data	No data	3,970	4,130	No data	4,130
Total	73	7,816	3,510	4,100	822,947	838,373	72,118	910,491

[a]Data in Toxic Release Inventory (TRI99 2002) are maximum amounts released by each facility.
[b]Postal Service state abbreviations are used.
[c]Sum of fugitive and stack releases is included in releases to air from given facility.
[d]Sum of all releases to air, water, underground injection wells, and land.
[e]Total amount transferred off site, including to publicly owned treatment works.
Source: ATSDR 2002.

TABLE 2-4 Industries That Use Beryllium

Industry	Products
Aerospace	Altimeters; braking systems; bushings, bearings for landing gear; electronic, electric connectors; engines; gyroscopes; mirrors (for example, in space telescopes); precision tools; rockets; satellites; structural components
Automotive	Air-bag triggers; antilock-brake-system terminals; electronic, electric connectors; steering-wheel connecting springs; valve seats for drag- racing engines
Biomedical	Dental crowns, bridges, partials, other prostheses; medical laser, scanning-electron-microscope components; x-ray tube windows
Defense	Heat shields; mast-mounted sights; missile guidance systems; nuclear-reactor components, nuclear triggers; submarine hatch springs; tank mirrors

(Continued)

TABLE 2-4 Continued

Industry	Products
Energy, electricity	Heat-exchanger tubes; microelectronics; microwave devices; nuclear-reactor components; oil-field drilling, exploring devices; relays, switches
Fire prevention	Nonsparking tools; sprinkler-system springs
Instruments, equipment, objects	Bellows; camera shutters; clock, watch gears, springs; commercial speaker domes; computer disk drives; musical-instrument valve springs; pen clips; commercial phonograph styluses
Manufacturing	Injection molds for plastics
Sporting goods, jewelry items	Golf clubs; fishing rods; naturally occurring beryl and chrysoberyl gemstones, such as aquamarine, emerald, alexandrite; man-made gemstones, such as emeralds with distinctive colors
Scrap recovery, recycling	Various beryllium-containing products
Telecommunication	Cellular-telephone components; electromagnetic shields; electronic, electric connectors; personal-computer components; rotary-telephone springs, connectors; undersea repeater housings

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TOXICOKINETICS

As is true of most metal compounds, the pulmonary deposition and disposition of inhaled beryllium compounds vary with solubility and particle size. EPA (1998b) did not identify any human studies of the deposition or absorption of inhaled beryllium but provided a review of the available animal studies. A more detailed review was provided by ATSDR (2002). The more soluble compounds are generally cleared more rapidly by dissolution in respiratory tract fluid. Insoluble particles deposited in the upper respiratory tract and tracheobronchial tree are cleared by mucociliary transport; those deposited in the pulmonary regions are cleared by a number of mechanisms and pathways, primarily by alveolar macrophages. The clearance of insoluble compounds from the lungs has been generally shown to be biphasic, with clearance half-times of days (by mucus transport and alveolar macrophages) to years (by dissolution and other translocation mechanisms) (Schlesinger 1995; NCRP 1997). Animal studies have demonstrated very slow pulmonary clearance of beryllium oxide (Sanders et al. 1975; Rhoads and Sanders 1985). In humans, residence times in the lungs are assumed to be years on the basis of the presence of insoluble beryllium many years after cessation of occupational exposure (ATSDR 2002).

Substantial fractions of inhaled beryllium doses can be removed by mucociliary clearance, enter the gastrointestinal tract, and be excreted in the feces. Fecal excretion dominates because gastrointestinal absorption of even water-soluble forms of beryllium is low. In rodents and dogs, urinary-excretion data indicated that less than 1% of an oral dose was absorbed; in monkeys, less than 4% was absorbed and excreted in the urine (Furchner et al. 1973). The small fraction of inhaled beryllium that is cleared from the lungs and absorbed into the systemic circulation is distributed primarily to the skeleton, liver, and tracheobronchial lymph nodes.

REVIEW OF EXPOSURE DATA

Naturally Occurring and Background Exposure

This section reviews available information on the nature and magnitude of and variation in exposure via diet, drinking water, soil contact, and inhalation. As described above, naturally occurring concentrations of beryllium in air are very low, although higher concentrations would be expected around coal-fired power plants and other facilities that emit beryllium. Cigarette smoke contains various low amounts of beryllium (ATSDR 2002). Beryllium in cigarette smoke has been reported to range from 0 to

0.0005 µg/cigarette (Smith et al. 1997). Beryllium was detected in only four of the 12 studies in which it was a target element (Smith et al. 1997). During the early 1970s, increased aerosolized beryllium from newly ignited camp-lantern mantles was reported; the mantles reportedly contained up to 600 µg of beryllium, most of which was volatilized soon after ignition (Griggs 1973).

Average concentrations of beryllium in U.S. tapwater and bottled water are reported to be 0.013 and less than 0.1 µg/L, respectively (ATSDR 2002). Beryllium is also present in grains and produce at generally low (nanograms per gram) fresh-weight concentrations (ATSDR 2002); however, reliable estimates of daily dietary intake have not been reported.

Exposure in the Air Force

At one of the committee's meetings, the Air Force presented data on its beryllium exposure assessments (DeCamp 2007). In the period July 2003-September 2006, the Air Force analyzed 3,386 personal and area air samples taken from 95 installations and found that 29 (1%) exceeded the laboratory reporting limit of 0.025 µg. Time-weighted averages for samples with detectable beryllium ranged from 0.02 to 0.29 $\mu g/m^3$; the samples were taken from the following processes: welding aircraft or vehicle parts (six samples), weapons fire at an indoor range (five samples), installing or removing aircraft panels (four samples), jackhammering cement and torching rebar (four samples), priming or spray painting aircraft parts (two samples), processing dental implants (two samples), recovery of aircraft parts after a crash (two samples), lapping copper-beryllium alloy bushings (one sample), bead blasting (one sample), sanding aircraft parts (one sample), and cutting and brazing (one sample). Surface samples were also taken in September 2003-August 2006. Of the 684 samples from 28 installations analyzed, 50 (7%) exceeded the laboratory reporting limit of 0.025 µg. Results of surface samples above the laboratory reporting limit for beryllium ranged from 0.034 to 1,160 µg per sample.

While these data would suggest that beryllium exposures in the Air Force are generally low, it is important to note that most samples were collected as part of a general dust and metals sampling effort that did not specifically target beryllium. Some job tasks, such as cutting fuselages into pieces for transport after an aircraft crash, are sporadic and may not be routinely sampled, while other job tasks, such as welding or sanding, although performed regularly, may have sporadic beryllium exposure. Building upon Air Force sampling data to date, a systematic and target beryllium sampling effort is needed to fully evaluate beryllium exposures in the Air Force.

Other Occupational Exposure

Inhalation-Exposure Studies

Table 2-5 summarizes historical airborne-beryllium exposure studies. Studies have been conducted in beryllium mines, metal-processing and production facilities, alloying facilities, and nuclear-weapons facilities. Exposure data dating back to the 1930s and 1940s are available.

The following observations can be garnered from the literature summarized in Table 2-5:

- Exposure in the early years of beryllium production and use was often in excess of the 2-$\mu g/m^3$ exposure limit, and exposure at 100-1,000 times the current concentrations was not unusual. For example, Sanderson et al. (2001a) reported on daily-weighted-average exposure in a beryllium-copper alloy plant dating back to 1935 that was generally 10-100 $\mu g/m^3$. Stefaniak et al. (2003a) reported on exposure at Los Alamos National Laboratory (LANL) dating back to the 1940s that averaged 32 $\mu g/m^3$.

TABLE 2-5 Summary of Beryllium Airborne-Exposure Studies

Reference	Setting	Sample Type	Summary of Key Findings	Comments
Taiwo et al. 2008	Aluminum smelters	Personal	Unspecified Jobs *2000-2005* Range, 0.0002 µg/m^3-13 µg/m^3 Mean, 0.22 µg/m^3 Median, 0.05 µg/m^3	
Madl et al. 2007	Beryllium-metal machining plant	Personal	Machining *1980-1995* Mean, 1.63 µg/m^3 Median, 0.33 µg/m^3 11% of samples, >2 µg/m^3 *1996-1999* Mean, 0.45 µg/m^3 Median, 0.16 µg/m^3 1.8% of samples, >2 µg/m^3 *2000-2005* Mean, 0.11 µg/m^3 Median, 0.09 µg/m^3 No samples, >2 µg/m^3 Nonmachining *1980-1995* Mean, 1.01 µg/m^3 Median, 0.12 µg/m^3 14% of samples, >2 µg/m^3 *1996-1999* Mean, 0.22 µg/m^3 Median, 0.08 µg/m^3 No samples, >2 µg/m^3 *2000-2005* Mean, 0.08 µg/m^3 Median, 0.06 µg/m^3 No samples, >2 µg/m^3	
		Area	Processing *1980-1995* Mean, 0.20 µg/m^3 Median, 0.20 µg/m^3 11% of samples, >2 µg/m^3 *1996-1999* Mean, 0.06 µg/m^3 Median, 0.06 µg/m^3 No samples, >2 µg/m^3	

			2000-2005 Mean, 0.08 µg/m^3 Median, 0.04 µg/m^3 No samples, >2 µg/m^3 Nonprocessing *1980-1995* Mean, 0.04 µg/m^3 Median, 0.05 µg/m^3 No samples, >2 µg/m^3 *1996-1999* Mean, 0.04 µg/m^3 Median, 0.04 µg/m^3 No samples, >2 µg/m^3 *2000-2005* Mean, 0.04 µg/m^3 Median, 0.04 µg/m^3 No samples, >2 µg/m^3	
Kelleher et al. 2001	Machining facility	Personal	Individual lifetime weighted exposure, 0.08-0.6 µg/m^3	20 workers with BeS or CBD
Martyny et al. 2000	Precision machining plant	Point of operation	Mean, 7.19 µg/m^3 (TWA) Range, 0.02-122.32 µg/m^3 (TWA)	
		Nearest worker location	Mean, 0.91 µg/m^3 (TWA) Range, 0.01-18.13 µg/m^3 (TWA)	
		Personal impactor	Mean, 1.51 µg/m^3 (TWA) Range, 0.03-22.68 µg/m^3 (TWA)	
		Total beryllium	Mean, 1.48 µg/m^3 (TWA) Range, 0.03-41.48 µg/m^3	
Cummings et al. 2007	Beryllium oxide ceramics facility	Personal	Production *1994-1999* Range, <0.02-62.4 µg/m^3 Median, 0.20 µg/m^3 GM, 0.21 µg/m^3 2% of samples, >2 µg/m^3 55% of samples, >0.2 µg/m^3 *2000-2003* Range, <0.02-53.3 µg/m^3 Median, 0.18 µg/m^3 GM, 0.18 µg/m^3 4% of samples, >2 µg/m^3 50% of samples, >0.2 µg/m^3	

(Continued)

TABLE 2-5 Continued

Reference	Setting	Sample Type	Summary of Key Findings	Comments
Cummings et al. 2007 *(continued)*	Beryllium oxide ceramics facility	Personal	<u>Production support</u> *1994-1999* Range, <0.02-0.80 µg/m^3 Median, 0.10 µg/m^3 GM, 0.11 µg/m^3 <1% of samples, >2 µg/m^3 29% of samples, >0.2 µg/m^3 *2000-2003* Range, <0.02-7.70 µg/m^3 Median, 0.04 µg/m^3 GM, 0.04 µg/m^3 <1% of samples, >2 µg/m^3 12% of samples, >0.2 µg/m^3 <u>Administration</u> *1994-1999* Range, <0.20 µg/m^3 *2000-2003* Range, <0.02-0.35 µg/m^3 Median, 0.02 µg/m^3 GM, 0.02 µg/m^3 <1% of samples, >2 µg/m^3 <1% of samples, >0.2 µg/m^3	
Hennenberger et al. 2001	Ceramics plant	Area	1.7% of samples, >2 µg/m^3 0.6% of samples, >5 µg/m^3 0.2% of samples, >25 µg/m^3	Sampling, 1981-1998
		Breathing zone	6.4% of sample, >2 µg/m^3 2.4% of samples, >5 µg/m^3 0.3% of samples, >25 µg/m^3	
Kreiss et al. 1996	Beryllia ceramics plant	Area	Machining median, 0.3 µg/m^3 (n = 58) Other areas median, <0.1 µg/m^3 (n = 865)	1981-1992 historical data
		Breathing zone	Machining median, 0.6 µg/m^3 (n = 130) Other areas median, <0.3 µg/m^3 (n = 636)	
		Daily weighted average	Machining median range, 0.1-0.9 µg/m^3 Kiln operator median, 0.3 µg/m^3 Lapping median, 0.6 µg/m^3	Highest exposure for machining job of sawing, grinding

Day et al. 2007	Alloy strip, wire finishing	Area	GM, 0.003 µg/m^3; GSD, 3.4 Range, 0.007-0.02 µg/m^3	72-h TWA
Stanton et al. 2006	Copper-beryllium distribution centers	Personal	<u>Production of bulk products</u> Range, <0.02-1.62 µg/m^3 Median, 0.04 µg/m^3 GM: 0.04 µg/m^3 <1% of samples, >2 µg/m^3 9% of samples, >0.2 µg/m^3 <u>Production of strip metal</u> Range, <0.01-1.40 µg/m^3 Median, 0.03 µg/m^3 GM, 0.03 µg/m^3 <1% of samples, >2 µg/m^3 2% of samples, >0.2 µg/m^3 <u>Production support</u> Range, <0.02-0.13 µg/m^3 Median, 0.01 µg/m^3 GM, 0.02 µg/m^3 <1% of samples, >2 µg/m^3 <1% of samples, >0.2 µg/m^3 <u>Administration</u> Range, <0.02-0.32 µg/m^3 Median, 0.01 µg/m^3 GM, 0.02 µg/m^3 <1% of samples, >2 µg/m^3 2% of samples, >0.2 µg/m^3	
Schuler et al. 2005	Copper-beryllium alloy processing	Personal	<u>Production of rod and wire</u> Range, <0.01-7.80 µg/m^3 Median, 0.06 µg/m^3 <1% of samples, >2 µg/m^3 24% of samples, >0.2 µg/m^3 <u>Production of strip metal</u> Range, <0.01-0.72 µg/m^3 Median, 0.02 µg/m^3 <1% of samples, >2 µg/m^3 <1% of samples, >0.2 µg/m^3 <u>Production support</u> Range, <0.01-0.33 µg/m^3 Median, 0.02 µg/m^3	

(Continued)

TABLE 2-5 Continued

Reference	Setting	Sample Type	Summary of Key Findings	Comments
Schuler et al. 2005	Copper-beryllium alloy processing	Personal	Production support *(continued)* <1% of samples, >2 µg/m^3 2% of samples, >0.2 µg/m^3 Administration Range, <0.01-0.11 µg/m^3 Median, 0.02 µg/m^3 <1% of samples, >2 µg/m^3 <1% of samples, >0.2 µg/m^3	Sampling, 1977-2000
Yoshida et al. 1997	Beryllium-copper alloy plants	Area	Plant 1 alloy process, GM range, 1992-1995, 0.16-0.26 µg/m^3; maximum, 1.85 µg/m^3 Plant 1 process without beryllium, GM range, 1992-1995, 0.01-0.02 µg/m^3 Plant 2 alloy cold rolling, drawing, heat treatment, GM range, 1993-1995, 0.03-0.19 µg/m^3; maximum, 0.28 µg/m^3 Plant 2 processes without beryllium, <0.01 µg/m^3	
Kreiss et al. 1997	Beryllium, beryllium-alloy plant	Area	Median, 0.4 µg/m^3 Range, 0.1-0.7 µg/m^3 Pebble plant median, 0.4 µg/m^3 Pebble plant range, 0.1-79.2 µg/m^3	1984-1993 historical data
		Breathing zone	Median, 1.4 µg/m^3 Range, 0.1-2.0 µg/m^3 Pebble plant median, 1.1 µg/m^3 Pebble plant range, 0.1-293.3 µg/m^3	
		Personal	Median, 1.0 µg/m^3 Range, 0.1-52.6 µg/m^3 Beryllium oxide production median, 3.8 µg/m^3 Alloy melting, casting median, 1.75 µg/m^3 Arc-furnace workers median, 1.75 µg/m^3 Pebble plant median, 0.9 µg/m^3 Pebble plant range, 0.1-19.0 µg/m^3	
		Daily weighted average	Range, 0.5-63.11 µg/m^3 Arc-furnace workers median, 1.65 µg/m^3 Furnace rebuild workers median, 1.63 µg/m^3 Pebble plant median, 0.7 µg/m^3 Pebble plant range, 0.1-7.9 µg/m^3	1984-1993 historical data Quarterly estimates based on area, breathing zone, personal samples

Rosenman et al. 2005	Processing facility, PA	Daily weighted average	Mean average range, 7.1-8.7 μg/m^3 Mean peak range, 53-87 μg/m^3 Mean cumulative range, 100-209 μg/m^3	Exposure data presented in relation to subjects classified with BeS or CBD or as normal
Stefaniak et al. 2003a	DOE LANL	Area, personal	1940s, 31.94 μg/m^3 (mean) 1950s, 2.3 μg/m^3 (mean) 1960s, 0.25 μg/m^3 (mean) 1970s, 1.34 μg/m^3 (mean) 1980s, 2.36 μg/m^3 (mean)	Historical data
Mitchell and Hyatt 1957	DOE LANL	Area	98% of samples, <1.0 μg/m^3 2% of samples, 1.0-25 μg/m^3	Machine-shop sampling, 1952-1956, highly controlled environment
		Shop stack samples	6% of samples, 1.0-25 μg/m^3	
Deubner et al. 2001a	Mining, mill facility; products facility; ceramics facility	Area	Mining, milling, 0.3-1.9 μg/m^3 (annual medians) Mining, milling annual maximums, 6.2-234.5 μg/m^3 Mixed-product production, 0.1-1.0 μg/m^3 (annual medians) Ceramic production, 0.1-0.4 μg/m^3 (annual medians)	1970-1999 historical data
		Breathing zone	Mining, milling, 0.3-15.9 μg/m^3 (annual medians) Mixed-product production, 0.7-2.1 μg/m^3 (annual medians) Ceramic production, 0.1-0.9 μg/m^3 (annual medians)	
		Daily weighted averages	Mining, milling, 0.08-0.2 μg/m^3 (annual medians) Mixed-product production, 0.1-2.5 μg/m^3 (annual medians) Ceramic production, 0.1-0.5 μg/m^3 (annual medians)	Based on general area, breathing-zone samples
		Personal	Mining, milling, 0.05-0.8 μg/m^3 Mining, milling annual maximums, 0.04-165.7 μg/m^3	
Johnson et al. 2001	Cardiff Atomic Weapons Plant	Area	Annual mean range, 0.02 (1997) to 0.32 μg/m^3 (1985) Annual maximum range, 7.02 (1997) to 1,128 μg/m^3 (1985) Foundry mean range for entire period, 0.05-0.39 μg/m^3 Old machine-shop mean range for entire period, 0.01-0.05 μg/m^3 New machine-shop mean range for entire period, 0.02-0.01 μg/m^3	1981-1997 historical data
		Personal	Annual mean range, 0.12 (1997) to 0.28 μg/m^3 (1984) Annual 95th percentile range, 0.22 (1997) to 1.1 μg/m^3 (1983) Overall mean, foundry workers, 0.87 μg/m^3 Overall mean, inspection workers, 0.22 μg/m^3	

(Continued)

TABLE 2-5 Continued

Reference	Setting	Sample Type	Summary of Key Findings	Comments
		Personal	Overall mean, laboratory workers, 0.22 μg/m^3 Overall mean, machine-shop workers, 0.32 μg/m^3 Overall mean, safety workers, 0.19 μg/m^3 Overall mean, service workers, 0.29 μg/m^3	
Apostoli and Schaller 2001	Metallurgy workers	Area	Steel-plant furnace area, 0.11μg/m^3 (median) Steel-plant casting area, 0.03 μg/m^3 (median) Copper-alloy plant furnace area, 0.4 μg/m^3 (median) Copper-alloy plant casting area, 0.2 μg/m^3 (median)	30 control workers, exposure not detected
Kent et al. 2001	Manufacturing plant, Elmore, OH	Personal	Total mass mean range, 0.13-1.04 μg/m^3 Alveolar deposition, 0.05-0.63 μg/m^3	Andersen impactor Ammonium beryllium fluoride, beryllium fluoride reduction furnace had highest concentrations
		Area	Total mass mean range, 0.85-2.74 μg/m^3 Alveolar deposition, 0.02-0.29 μg/m^3	Micro-orifice uniform deposit impactor Ammonium beryllium fluoride, beryllium fluoride reduction furnace had highest concentrations
Sanderson et al. 2001a	Beryllium plant, PA (lung cancer case-control study)	Daily weighted average	1935-1960, 1.7-767 μg/m^3 (mean) 1961-1970, 1.0-69 μg/m^3 (mean) 1971-1980, 0.1-3.1 μg/m^3 (mean) 1981-1992, 0.03-1.4 μg/m^3 (mean)	1935-1992 historical data
Viet et al. 2000	DOE Rocky Flats beryllium shop	Area	Annual mean ranges 1960s, 0.116-0.662 μg/m^3 1970s, 0.104-0.416 μg/m^3 1980s, 0.083-0.271 μg/m^3 Maximum daily ranges 1960s, 3.49-36.80 μg/m^3 1970s, 1.57-11.34 μg/m^3 1980s, 0.54-20.00 μg/m^3	Machine-shop sampling, 1960-1988
Barnard et al. 1996	DOE Rocky Flats beryllium shop	Area	1970-1974, 0.34 μg/m^3 (weighted mean) 1975-1982, 0.14 μg/m^3 (weighted mean) 1983-1986, 0.2 μg/m^3 (weighted mean) 1987-1988, 0.04 μg/m^3 (weighted mean)	Retrospective reconstruction, 62% of samples below detection limit
		Personal	1984-1987, 0.79 μg/m^3	6- 8-h TWA

Stange et al. 1996a	DOE Rocky Flats, main production building	Area	Annual average range, 1970-1988, 0.03 µg/m^3 (1987) to 0.42 (1973)	Based on random sample of results
		Personal	Annual average range, 1984-1987, 0.19 (1987) to 1.2 µg/m^3 (1985)	
Stange et al. 1996b	DOE Rocky Flats, main production building	Fixed airhead	Annual mean ranges 1970-1979, 0.10-0.42 µg/m^3 1980-1988, 0.03-0.27 µg/m^3	
		Personal	Annual mean 1985, 1.09 µg/m^3 1986, 1.20 µg/m^3 1987, 0.46 µg/m^3 1988, 0.19 µg/m^3	
Seiler et al. 1996	Various facilities (five plants, PA, OH)	Area	Mean range, 0.3-2.0 µg/m^3 (n = 50)	1950-1978 historical data
		Breathing zone	Mean range, 0.4-25.6 µg/m^3 (n = 36)	
		Daily weighted average	Mean range, 0.3-4.8 µg/m^3	
Hoover et al. 1990	Sawing, milling of beryllium metal, alloys	Area	General work area, 0.07 µg/m^3 Ventilation shroud, >7,000 µg/m^3	Sawing, milling, grinding produced large particles (50-300 µm) PCAM
Kriebel et al. 1988	Extraction, manufacturing facility	Daily weighted average	1935-1954, 0.2-80 µg/m^3 1955-1964, 0.2-51 µg/m^3 1965-1976, 0.1-33 µg/m^3 1977-1983, 0.1-0.7 µg/m^3	1935-1983 historical data Assumed range of means
Cullen et al. 1987	Precious-metal refining	Personal	Mean, 1.2 ± 0.96 µg/m^3 (n = 114) Range, 0.22-42.3 µg/m^3 Crusher, 2.7 ± 7.2 µg/m^3 Ball-mill operators, 2.1 ± 1.6 µg/m^3	Samples collected, 1983
Cotes et al. 1983	Ore refining	Area	1952, 0.8 µg/m^3 (annual mean) 1960, 0.4 µg/m^3 (annual mean) Highest samples collected in final hydroxide plant, 1952, 2 µg/m^3) 9% of 3,000 samples, >2 µg/m^3	

(Continued)

TABLE 2-5 Continued

Reference	Setting	Sample Type	Summary of Key Findings	Comments
Donaldson and Stringer 1980	Beryllium-production facilities	Daily weighted average	Mean in powdered-metal products area, 1.55 ± 1.97 µg/m^3 (n = 105) Mean in extraction oxide area, 1.75 ± 2.16 µg/m^3 (n = 144) Mean in ceramics area, 1.03 ± 1.43 µg/m^3 (n = 36) Mean in alloy area, 2.93 ± 3.44 µg/m^3 (n = 54) Mean in maintenance area, 19.19 ± 66.36 µg/m^3 (n = 18)	Samples collected, 1974
		Personal total dust	Mean in powdered-metal products area, 1.02 ± 1.63 µg/m^3 (n = 105) Mean in extraction oxide area, 1.40 ± 1.26 µg/m^3 (n = 144) Mean in ceramics area, 0.75 ± 1.36 µg/m^3 (n = 36) Mean in alloy area, 1.58 ± 1.90 µg/m^3 (n = 54) Mean in maintenance area, 3.59 ± 9.85 µg/m^3 (n = 18)	
		Personal respirable dust	Mean in powdered-metal products area, 5.2 ± 10.73 µg/m^3 (n = 105) Mean in extraction oxide area, 2.63 ± 1.88 µg/m^3 (n = 144) Mean in ceramics area, 1.69 ± 3.06 µg/m^3 (n = 36) Mean in alloy area, 5.09 ± 6.75 µg/m^3 (n = 54) Mean in maintenance area, 12.96 ± 35.74 µg/m^3 (n = 18)	
Campbell 1961	High-explosives test facility	Area	Mean concentration in bunker range, 0.08-0.14 µg/m^3 Mean in control room, 0.07 µg/m^3 Mean in office, 0.04 µg/m^3	Test explosions produced soil contamination extending up to 200 ft from test site.
		Breathing zone	Mean concentration outside bunker, 0.11-2.4 µg/m^3	
Sussman et al. 1959	Nonoccupational	Ambient-air sampling	Median around plant, 0.004 µg/m^3 Median around steel mill collected for comparison, 0.0002 µg/m^3	500 2-day samples collected around beryllium plant, PA
Eisenbud et al. 1949	Nonoccupational	Ambient-air sampling, modeling	Average concentrations, 350-750 ft from plant, 0.05-0.15 µg/m^3 Highest concentration measured within 350 ft of plant, 2.1 µg/m^3	Based on investigations of berylliosis case near beryllium processing plant, Lorain, OH

ABBREVIATIONS: BeS, beryllium sensitization; CBD, chronic beryllium disease; DOE, U.S. Department of Energy; GM, geometric mean; GSD, geometric standard deviation; LANL, Los Alamos National Laboratory; PCAM, portable continuous aerosol monitor; TWA, time-weighted average.

- Exposure to beryllium has generally decreased. In 1930-1950, exposure typically ranged from micrograms per cubic meter to hundreds of micrograms per cubic meter; in 1950-1970, micrograms to tens of micrograms per cubic meter; in 1970-1980, tenths of a microgram to tens of micrograms per cubic meter; and in 1980-1990, from hundredths of a microgram to micrograms per cubic meter. That indicates a general trend, but it should be noted that beryllium exposure can vary considerably and that there was potential for exposure outside those general ranges.
- Beryllium exposure in a given facility is highly variable in terms of time-weighted averages and short-term exposure concentrations. Stefaniak et al. (2003a) indicate annual geometric standard deviations (GSDs) of 2-14 for exposures at LANL, Barnard et al. (1996) reported a coefficient of variation of 120% in personal exposure at Rocky Flats, and Day et al. (2007) report a GSD of 3.4 for area air samples collected in a copper-beryllium alloy facility.
- Hot process environments (such as foundry and furnace operations) in beryllium-production facilities generally have the highest exposure (Kriebel et al. 1988; Johnson et al. 2001; Sanderson et al. 2001a). In contrast, Cullen et al. (1987) reported that the highest exposure at a precious-metal refinery was associated with ball-mill and crusher job titles.
- Hydrolysis and wet grinding operations produced the highest exposure in mining and milling operations (Deubner et al. 2001a).
- Grinders, lappers, deburrers, and lathe operators have high exposure in beryllium-machining operations (Kelleher et al. 2001; Madl et al.2007). Kreiss et al. (1996) reported machining and lapping as high-exposure jobs at a beryllium ceramics plant.
- Annealing and pickling operations had the highest airborne beryllium concentrations at a copper-beryllium alloy producing facility (Schuler et al. 2005).
- Maintenance workers are at risk for high uncontrolled exposure (Donaldson and Stringer 1980; Stange et al. 1996b).
- Area samples underestimate exposure and do not correlate statistically with personal exposure (Donaldson and Stringer 1980; Barnard et al. 1996; Stange et al. 1996a; Johnson et al. 2001).

Skin-Exposure Studies

A consistent relationship between inhalation and BeS or CBD has been difficult to establish. Additional opportunities for exposure that have not been measured may contribute to the inconsistency. One possible additional exposure route is skin (Tinkle et al. 2003). It has been hypothesized that penetration of the skin by poorly soluble beryllium particles may be an immunologic route to sensitization, as can occur with skin contact and soluble beryllium salts. An early study by Curtis (1951) demonstrated that patch testing with soluble beryllium salts, but not beryllium metal or beryllium powder, elicited positive reactions in patients with contact dermatitis. To determine whether skin might be a route of exposure to particles, such as beryllium, Tinkle et al. (2003) demonstrated that 0.5- and 1.0-μm dextran beads in conjunction with motion, as at the wrist, penetrated the stratum corneum of explanted human skin and reached the epidermis and occasionally the dermis. In separate experiments, cutaneous application of beryllium oxide and beryllium sulfate generated a beryllium-specific, cell-mediated immune response in exposed susceptible mice. Day et al. (2006) hypothesized that skin exposure may cause BeS but that inhalation exposure is necessary for manifestation of CBD.

In a study to evaluate the efficacy of an improved particle-migration control program, beryllium was measured in workplace air, on work surfaces, on cotton gloves worn by employees over nitrile gloves, and on the necks and faces of employees after implementation of the program (Day et al. 2007). The geometric mean beryllium concentration in all general-area air samples was 0.003 $\mu g/m^3$ (range, 0.0007-0.02 $\mu g/m^3$). In production, production-support, and office areas, the geometric mean beryllium concentrations were, respectively, 0.95, 0.59, and 0.05 $\mu g/100\ cm^2$ on work surfaces; 42.8, 73.8, and 0.07 μg/sample on cotton gloves; 0.07, 0.09, and 0.003 μg on necks; and 0.07, 0.12, and 0.003 μg on faces.

Strong correlations were found between beryllium in air and on work surfaces (r = 0.79), on cotton gloves and on work surfaces (r = 0.86), on necks (r = 0.87), and on faces (r = 0.86). The study showed that even with the implementation of control measures to reduce skin contact with beryllium as part of a comprehensive workplace-protection program, measurable beryllium continued to reach the skin of workers in production and production-support areas.

Only a few studies apart from the study by Day et al. (2007) have reported measures of surface beryllium contamination and skin exposure (see Table 2-6). Sanderson et al. (1999) reported extensive beryllium contamination in vehicles and on the hands of machine-shop workers. Beryllium-containing particles on the skin and work clothing can potentially be transferred to the breathing zone or to the mucous membranes of the nose and mouth via hand-to-face or clothing-to-face contact. The contribution of this route of exposure is not captured or represented by breathing-zone air sampling. The systemic toxicity of ingested insoluble forms (metal, alloy, and oxide) is thought to be low, but the role of ingested beryllium in sensitization has not been evaluated.

The following can be tentatively concluded from the literature:

- Even in workplaces with stringent exposure controls, measurable beryllium can be detected on surfaces and the skin of workers.
- Surface and skin contamination appears to correlate with airborne beryllium concentration. Surface contamination can result in the spread of beryllium outside primary production or use areas.
- Skin is an exposure pathway that has been hypothesized to lead to sensitization (see Chapter 3 for further discussion).

Biomarkers of Exposure

Blood and urinary beryllium concentrations have been used for biologic monitoring of beryllium exposure, but their reliability and utility have been called into question (ATSDR 2002). Apostoli and Schaller (2001) stated that reference values reported earlier were too high because of poor specificity and sensitivity of the analytic methods. According to a review by Reeves (1986), studies in the middle 1980s and earlier reported blood and urinary beryllium concentrations in unexposed populations that were below the detection limit of analytic methods available at the time (1 µg/L), whereas in exposed populations beryllium varied from undetectable to 3 µg/L. As workplace exposures have been reduced, methods with lower detection limits have been applied with varied success in distinguishing between exposed and unexposed populations. In 1998, Paschal et al. (1998) reported urinary-beryllium data on 496 Americans collected from 1988 to 1994 in the third National Health and Nutrition Examination Survey (NHANES III). The mean value was 0.28 µg/L, which is consistent with values reported in other large, contemporary studies of unexposed populations (Minoia et al. 1990; Apostoli et al. 1992).

In contrast, two more recent studies have reported much lower values in small populations. Apostoli and Schaller (2001) reported urinary beryllium below the detection limit of 0.03 µg/L in 30 unexposed subjects, and Wegner et al. (2000) reported values below 0.06 µg/L in 30 gem cutters who spent little time working with beryls. In contrast, metallurgy workers investigated by Apostoli and Schaller had detectable urinary beryllium (median, 0.09 and 0.06 µg/L in electric steel-plant furnace and casting workers, respectively; 0.25 and 0.125 µg/L in copper-alloy foundry-furnace and casting workers, respectively), and urinary concentrations were reported to correlate with air beryllium concentrations. Wegner et al. (2000) also reported detectable urinary beryllium in many of the 27 gem cutters who worked regularly with beryls (preshift and postshift means, 0.13 and 0.08 µg/L, respectively). Considering that the urinary beryllium concentrations reported in those workers are similar to or lower than concentrations previously thought to be representative of the general population, additional studies with more recent analytic methods are needed. To date, no urinary or blood biomarkers have been shown to reflect workplace beryllium exposure accurately.

TABLE 2-6 Summary of Beryllium Skin-Exposure and Surface-Exposure Studies

Reference	Jobs or Worker Area	Sample Type	Summary of Key Findings	Comments
Emond et al. 2007	Recycling facility	Body-surface sample	Postexposure samples of skin, from below limit of detection to 0.26 μg/100 cm^2 Postexposure samples of coverall surfaces, 1.6-2.6 μg/100 cm^2	Skin concentrations were estimated to be 10^{-3} to 10^{-7} inhalation concentrations
Day et al. 2007	Alloy strip and wire finishing	Surface wipe	GM, 0.77 μg/100 cm^2	Large variability, GSDs range from 2.1 to 7.8 $n = 252$
			GM range, 0.05 μg/100 cm^2 (administrative area) to 13.6 μg/100 cm^2 (wire-annealing and pickling area)	
		Cotton glove	Overall GM, 13.4 μg/glove	Strong positive correlations between air and surface, surface and glove, glove and skin
			GM range, 0.07 μg/glove (administrative area) to 196.5 μg/glove (rod and wire production area)	
		Skin wipes	Overall GM on neck, 0.04 μg	
			Overall GM on face, 0.04 μg	
			GM range, 0.05 μg (administrative area) to 13.6 μg (wire annealing and pickling area)	
Sanderson et al. 1999	Machine shop	Wipe samples in vehicles	GM range, below detection limit (child car seat) to 19.0 μg/ft^2 (driver's side floor)	Machine-shop worker private vehicles
		Hand wipe	GM range, 1.0 μg/ft^2 (office worker) to 30.0 μg/ft^2 (E-cell worker)	
Campbell 1961	High-explosives test facility	Clothing samples	Maximum coverall contamination range, <19-159 μg/coverall	
			Maximum sock contamination, 178 μg/sock	
			Maximum shoe sample, 1.6 μg/cm^2	
		Surface samples	97% of samples in bunker (n = 145), <0.01 μg/cm^2	
			Mean of four detectable samples, 3.5 μg/cm^2	
Curtis 1951	Workers with dermatitis, controls	Patch testing	8 of 16 unexposed controls and all 13 beryllium-exposed workers responded positively to soluble beryllium compounds	
			No controls responded to insoluble forms of beryllium	
			3 beryllium workers responded positively to beryllium-metal powder	

ABBREVIATIONS: GM, geometric mean; GSD, geometric standard deviation.

REVIEW OF SAMPLING AND ANALYTIC METHODS

Beryllium-aerosol exposure-assessment methods have changed (Kolanz et al. 2001). The first air samples tested for beryllium were collected with electrostatic precipitators (Mitchell and Hyatt 1957). Filter-based sampling began in the early 1950s (Hyatt et al. 1959). Area or task-based area sampling strategies initially used high-volume pumps and filter-collection substrates, but more recent methods have adopted personal-sampling techniques. Three types of samples have been described: fixed-airhead

samples, high-volume samples, and personal samples (Hyatt and Milligan 1953; Lindeken and Meadors 1960; Campbell 1961; Kolanz et al. 2001). Fixed-airhead samples were collected at 10-100 L/min with open-faced samplers at fixed locations. High-volume samples were collected to estimate general area concentrations and to simulate personal exposures by placing a sampler in an employee's breathing zone and combining the results with time-activity information. High-volume samples were collected at 200-400 L/min on filter media. More recently, personal samples have been collected from the lapels of workers at 1-2 L/min. Size-selective air sampling has not been generally used for beryllium-exposure assessment. Most samples would have historically been considered as total dust samples, but it is important to recognize that all samplers have an inlet bias, and the use of the term *total dust* is now considered to be a misnomer. A comparison of respirable and total dust samples collected by Donaldson and Stringer (1980) indicated that total dust samples were 2-5 times more concentrated than respirable dust samples.

In the 1940s, beryllium was analyzed with spectrography (Cholak and Hubbard 1948). That technique had a relatively poor sensitivity of about 0.25 µg of beryllium. In the early 1950s, it was replaced with fluorometry that had a sensitivity of about 0.05 µg (Mitchell and Hyatt 1957). Flame atomic-absorption spectroscopic methods of detecting beryllium were introduced in the 1950s. Modern methods for detection use inductively coupled atomic-emission spectroscopy and plasma mass spectrometry (Brisson et al. 2006). Limits of detection of those methods and graphite-furnace atomic-absorption spectroscopy are 0.009, 0.001, and 0.005 µg/sample, respectively (Brisson et al. 2006).

In contrast with available air-sampling methods, there are few beryllium surface- and skin-exposure assessment methods. The available studies have used wipes to sample surface areas (Agrawal et al. 2006; Dufay and Archuleta 2006; Tekleab et al. 2006). Wipes have also been used to sample skin and clothing, and thin cotton gloves worn by workers have been used to assess hand exposure. The wipes or gloves have been digested and analyzed with the same spectroscopic techniques used for air-sample analysis. Surface-sampling results are typically expressed as micrograms per 100 cm^2 or micrograms per body part (such as the face) or glove. On-site direct-read portable detection systems have been developed and are being evaluated for surface beryllium assessment (Agrawal et al. 2006; Tekleab et al. 2006). None of these techniques has gained wide acceptance (Brisson et al. 2006).

EXPOSURE METRICS

The precise exposure-response relationship between beryllium and development of CBD has remained unclear, probably because of both the uncertainty in beryllium exposure and the specific immunologic mechanisms of CBD. The variable characterization of beryllium exposure also makes comparison between studies difficult.

Understanding of the role of dose in CBD is complicated by several exposure measures, including the airborne concentration of beryllium, the duration of exposure, and the solubility, particle size, and type of beryllium being manufactured or machined. Particle size, surface area, number, and concentration—particularly of submicrometer particles—are the most important dimensions to be determined. Because of the low density of beryllium, large particles would be aerodynamically smaller than other metal particles. It is important to characterize the size of airborne particles aerodynamically, and this should be followed by their chemical characterization. The solubility of beryllium compounds in skin, interstitial lung fluid, and phagolysosomes may also influence the bioavailability of beryllium.

Physical and Chemical Properties

Table 2-7 shows the physical and chemical properties of beryllium and commonly used beryllium compounds. Most beryllium compounds are poorly soluble in water. The most common compound used in industry is beryllium oxide; its solubility in water decreases as the temperature at which it is calcined

increases (Spencer et al. 1968; Novoselova and Batsanova 1969; Eidson et al. 1984). Beryllium carbonate and beryllium hydroxide are practically insoluble in water. Beryllium chloride, beryllium fluoride, beryllium nitrate, beryllium phosphate (trihydrate), and beryllium sulfate (tetrahydrate) are soluble in water. Beryllium carbonate and beryllium sulfate are formed during the extraction of beryllium hydroxide from ore. Beryllium ammonium fluoride and beryllium fluoride are formed during the processing of beryllium hydroxide to beryllium metal.

Concentration and Types of Beryllium in the Workplace

This section describes the concentrations and types of beryllium exposure in workplaces. Much of the information was ascertained as part of epidemiologic studies of BeS and CBD. Chapter 3 discusses the studies and the relationships found between specific exposures and BeS or CBD in more detail.

Beryllium concentrations in a workplace vary substantially according to the production process and differ from location to location within a factory at any given time. Workers are exposed not only to freshly generated particles from production processes but to particles mechanically resuspended from work surfaces and clothing fabric. Other factors, such as the ventilation system and the use of local exhaust hoods, also influence exposure concentrations. A cross-sectional study of a beryllium-ceramics plant and a multifaceted beryllium-production facility confirmed that the risk of BeS or CBD is process-related (Kreiss et al. 1997), but no association between cumulative or average exposure to beryllium and BeS was found. In contrast, a study by Viet et al. (2000) provided evidence of increasing risk of CBD with increasing cumulative beryllium exposure. Differences in physicochemical factors that potentially influence bioavailability of beryllium—including particle size, specific surface area (SSA), and chemical composition—might explain differences in study results.

TABLE 2-7 Physical and Chemical Properties of Beryllium and Beryllium Compounds

Name	Chemical Formula	Molecular Weight	Melting Point (°C)	Boiling Point (°C)	Density (g/cm^3)	Solubility in Water
Beryllium metal	Be	9.012	1,287-1,292	2,970	1.846	Insoluble
Beryllium oxide	BeO	25.01	2,508-2,547	3,787	3.016	Insoluble
Beryllium sulfate	$BeSO_4$	105.07	550-600 (decomposes)	Not applicable	2.443	Insoluble in cold water, decomposes in hot water
Beryllium carbonate (basic)	$Be(CO_3)_2$	112.05	No data	No data	No data	Insoluble in cold water, decomposes in hot water
Beryllium hydroxide	$Be(OH)_2$	43.03	Decomposes (loses H_2O)	Not applicable	1.92	3.44 mg/L
Beryllium nitrate (tetrahydrate)	$Be(NO_3)_2$	205.08	60.5	142 (decomposes)	1.557	1.66×10^6 mg/L
Beryllium phosphate (trihydrate)	$Be_3(PO_4)_2$	271.03	100 (decomposes, loses H_2O)	No data	No data	Soluble
Beryllium fluoride	BeF_2	47.01	555	1,175	1.986	Very soluble
Beryllium chloride	$BeCl_2$	79.92	405	520	1.899	Very soluble

Sources: Lide 1991; ATSDR 2002.

Exposure concentration can be measured with a personal sampler (usually on the lapel of work clothing) to sample for a full workshift and to collect samples of different atmospheres to which a worker is exposed during a shift. A number of investigators have concluded that area samples do not accurately reflect personal exposure (Barnard et al. 1996; Seiler et al. 1996). When area samples are combined with results of a simultaneous time-motion study of a worker, one can obtain an estimated time-weighted average. An average ratio of about 3:1 was found when exposure measured with personal lapel monitors was compared with exposure estimated by using area monitoring and time-motion studies (Cohen 1991). Placement of the monitors, fluctuations in flow rate of the sampling pumps, resuspension of dust from work clothing into lapel monitors, and complex spatial variability may have contributed to the discrepancy.

The dose of inhaled dust in an industrial setting can be influenced by several factors, such as dust concentration, particle size distribution, and breathing pattern. Because the biologic effects of inhaled aerosols depend on particle size and because many occupational diseases are associated with deposition of materials in particular regions of the respiratory tract, the American Conference of Governmental Industrial Hygienists has recommended particle-size–selective Threshold Limit Values for dozens of chemical substances (ACGIH 2007).

Cohen et al. (1983) used a multicyclone sampler to measure the size mass distribution of the beryllium aerosol at a beryllium-copper alloy casting operation. The mass median aerodynamic diameter (MMAD) ranged from 3 to 6 μm during most of the sampling period. For two measurement periods during which the furnace was being "charged," the MMAD was considerably larger (6-16 μm), probably because of resuspension of settled dust.

Hoover et al. (1990) reported that milling at a depth of 50 μm, compared with sawing, produced a smaller MMAD of beryllium particles. The milling process also produced a higher proportion of particles with MMAD smaller than 5 μm (9%) than did sawing (0.3%). In addition, the peak concentrations of beryllium particles captured by ventilation shrouds exceeded 7 mg/m^3 when beryllium metal was processed, whereas the concentrations were lower by a factor of 10 when beryllium alloys were used.

Several cross-sectional studies have demonstrated that some industrial processes are strongly associated with the development of CBD. A prevalence of 16% was associated with ceramics dry pressing (Kreiss et al. 1993a), 14% with ceramics machining (Kreiss et al. 1996), and 19% with beryllium-metal production (Kreiss et al. 1997); all those were higher than the prevalence of 5% in machinists in the nuclear industry (Kreiss et al. 1993b). Those data imply that the compositions of beryllium-containing aerosols derived with different processes or based on measures other than mass concentration may be responsible for the development of CBD.

To investigate risk factors other than mass concentration, Martyny et al. (2000) characterized particle size distribution associated with a number of beryllium-machining processes during normal operating procedures in a precision beryllium-machining plant that used cascade impactors. Table 2-8 shows the concentrations and particle sizes obtained with different operations in the plant. There were large differences between sampling locations. The data show that beryllium machining as performed in industry today produces a large number of fine respirable beryllium particles, of which more than 50% of the mass in the breathing zone of the worker consists of particles smaller than 10 μm and more than 30% smaller than 0.6 μm. Using the Andersen cascade impactor, Thorat et al. (2003) found similar size distribution; the mean MMAD of beryllium particles observed in various operations ranged from 5.0 to 9.5 μm.

Kent et al. (2001) used an Andersen impactor for personal sampling and a micro-orifice uniform deposition impactor (MOUDI) for area sampling; the prevalences of CBD and BeS were significantly associated with the mass concentration of particles smaller than 10 and 3.5 μm (collected with a MOUDI) but not associated with particles collected with the Andersen impactor. The placement of the monitors, fluctuations in flow rate of the sampling pumps, and resuspension of dusts from work clothing into lapel monitors might have contributed to the discrepancies (Cohen 1991). The estimated number and surface area concentration (with the MOUDI) of particles smaller than 10 μm deposited in the alveoli also

TABLE 2-8 Comparison of Beryllium Concentrations and Particle Sizes Obtained with Different Operations in a Precision Machining Plant

	Point of Operation[a]		Near Worker Location[a]		Personal Impactor[b]		Total[c]
Process	Median Concentration ($\mu g/m^3$)	MMAD (μm)	Median Concentration ($\mu g/m^3$)	MMAD (μm)	Median Concentration ($\mu g/m^3$)	MMAD (μm)	Median Concentration ($\mu g/m^3$)
Deburring	0.58	3.2	0.26	1.2	0.74	1.6	1.42
Grinding	2.21	4.1	0.65	2.3	0.34	3.1	0.47
Lapping	0.32	2.6	0.11	1.2	0.13	2.3	0.31
Lathe operation	4.08	3.6	0.27	0.6	0.60	0.6	1.01
Milling	0.18	5.3	0.18	0.6	0.25	2.7	0.52

[a]Samples taken with Lovelace Multijet Impactors.
[b]Samples taken with Series 290 Marple Personal Cascade Impactors.
[c]Samples taken with lapel samplers: closed-face 37-mm cassette with 0.8-µm-pore cellulose ester filter.
Source: Adapted from Martyny et al. 2000. Adapted table printed with permission; copyright 2000, *Journal of Occupational and Environmental Medicine*.

showed significant relationships with CBD. That no other exposure measures showed significant relationships with CBD or BeS suggests that size-selective characterization of exposure concentrations may provide more relevant exposure metrics for predicting the incidence of CBD or BeS than does the total mass concentration of airborne beryllium.

McCawley et al. (2001) tested the hypothesis that particle number would be more reflective of target organ dose than would particle mass and would be a more appropriate measure of exposure in connection with CBD. Area mass-based and number-based size distribution measurements were taken with a MOUDI and a scanning mobility particle sizer, respectively. Both the particle number and the mass distribution were weighted heavily with ultrafines for several processes; the fluoride-furnace area had the greatest number concentration (up to 10^9 particles/cm^3). There was no correlation between any measure of particle-mass dose and particle-number dose. Because most epidemiologic studies of health risks posed by beryllium measured only mass concentration of beryllium, more rigorous investigation is needed to establish the particle-number hypothesis.

In a case-control analysis of workers in a contemporary precision beryllium-machining plant, Kelleher et al. (2001) used personal sampling with total and particle-size fractions to investigate the relationship between beryllium exposure and health effects. Cases were more likely than controls to have worked as machinists (odds ratio, 4.4; 95% confidence interval, 1.1-17.6). The exposure concentrations at which workers developed CBD and BeS were mostly below the Occupational Safety and Health Administration's current permissible exposure limit of 2 $\mu g/m^3$; that suggests that the current limit does not completely protect workers from beryllium-related health effects. Although it is not statistically significant, the median cumulative total exposure was consistently higher in the cases (2.9 $\mu g/m^3$-year) than in the controls (1.2 $\mu g/m^3$-year). Median cumulative exposure of cases and controls to particles smaller than 6 µm in diameter was 1.7 $\mu g/m^3$-year and 0.5 $\mu g/m^3$-year, respectively.

Stefaniak et al. (2003b) investigated the particle structure and surface area of particles (powder and process-sampled) of beryllium metal, beryllium oxide, and copper-beryllium alloy that were separated by aerodynamic size. Their chemical compositions and structures were determined with x-ray diffraction and transmission electron microscopy, respectively. The beryllium-metal powder consisted of compact particles, whereas the beryllium oxide powder and alloy particles were clusters of smaller primary particles. The SSA of all samples varied by a factor of 37, from 0.56 m^2/g (the 0.4- to 0.7-µm fraction of the process-sampled reduction-furnace particles) to 20.8 m^2/g (the 0.4-µm or less fraction of the metal powder). Large relative differences in SSA were observed as a function of particle size of the beryllium-metal powder, from 4.0 m^2/g (particles larger than 6 µm) to 20.8 m^2/g (particles 0.4 µm or

smaller). In contrast, little relative difference (less than 25%) in SSA was observed as a function of particle size of the beryllium oxide powder and particles collected from the screening operation. The SSA of beryllium-metal powder decreases with increasing particle size, as expected for compact particles, and the SSA of the beryllium oxide powders and particles remains constant as a function of particle size, which might be expected for clustered particles. Those associations illustrate how process-related factors can influence the structure and SSA of beryllium materials. Structure and SSA may be important determinants of the bioavailability of beryllium and the associated risk of CBD.

Schuler et al. (2005) examined the prevalences of BeS and CBD and relationships between BeS and CBD and work-area processes and found that among 185 employees (153, or 83%, of whom participated), the prevalences of BeS and CBD were 7% (10 of 153) and 4% (six of 153), respectively. The prevalence of sensitization among employees with 1 year or less since first exposure was higher (13%); none of them had CBD. CBD risk was highest in rod- and wire-production workers; their air concentrations were highest.

The area of wire annealing and pickling had the highest airborne beryllium concentrations and may have been a source of exposure of workers in other rod and wire processes nearby. During the wire-annealing process, the formation and removal of loose oxide scale could disperse beryllium into the air and onto surfaces in work areas.

Bioavailability

Several studies have shown that the solubility and toxicity of the beryllium oxide particles are inversely proportional to the calcining temperature. To elucidate the role of solubility in the expression of beryllium toxicity, Finch et al. (1988) measured the dissolution kinetics of beryllium compounds calcined at different temperatures in 0.1 N HCl or simulated serum ultrafiltrate (SUF). Beryllium oxide calcined at 500°C had 3.3 times greater SSA than beryllium oxide calcined at 1000°C, although there was no difference in size or structure of the particles as a function of calcining temperature. The beryllium-metal aerosol, although similar to the beryllium oxide aerosols in aerodynamic size, had an SSA about 30% that of the beryllium oxide calcined at 1000°C. HCl was associated with a higher beryllium-dissolution rate than SUF, and the beryllium oxide aerosol calcined at 500°C was more soluble than the 1000°C-calcined aerosol in both solvents. The aerosols were much more soluble in HCl than in SUF over the 31-day study. Less than 10% of the beryllium in any form dissolved in SUF, whereas more than 99% of the 500°C-calcined beryllium oxide aerosol, 50% of the 1000°C-calcined beryllium oxide aerosol, and 64% of the beryllium-metal aerosol dissolved in HCl. On the basis of those data, the solubility constant (k, in grams per square centimeter-day) in SUF of beryllium metal, beryllium oxide calcined at 500°C, and beryllium oxide calcined at 1000°C was estimated at $(1.5 \pm 0.8) \times 10^{-9}$, $(2.2 \pm 0.5) \times 10^{-9}$, and $(3.7 \pm 1.2) \times 10^{-9}$, respectively. In a later study, beryllium oxide calcined at 1000°C, because of its low solubility, elicited little local pulmonary immune response whereas the much more soluble beryllium oxide calcined at 500°C produced a beryllium-specific, cell-mediated immune response in dogs (Haley 1991).

In a study of beryllium cellular dosimetry, Eidson et al. (1991) found that soluble beryllium sulfate was not taken up by beagle macrophages whereas 60% of added insoluble beryllium oxide was taken up; uptake was maximal after 6 h. The uptake was independent of calcining temperature. About 22% of 500°C-calcined beryllium oxide dissolved within 48 h after addition to cell culture; 39% of cells died in that period. Dissolved beryllium remained associated with cells until a cytotoxic concentration was reached (2.2×10^{-5} M; 15 nmol of beryllium per 10^6 cells), at which time the beryllium was released into the medium. There was no significant dissolution of the 1000°C-calcined beryllium oxide within 48 h and no significant cell death. The results indicate that beryllium dissolved from phagocytized beryllium oxide was more cytotoxic than soluble beryllium added extracellularly. Similar results were observed in a murine monocyte cell line (Day et al. 2005).

At the cellular level, beryllium dissolution must occur for the macrophage to present beryllium as an antigen to induce the cell-mediated CBD immune reactions (Stefaniak et al. 2006). In a

phagolysosomal-simulating fluid with a pH of 4.5, dissolution of both beryllium metal and beryllium oxide was greater than that previously reported in water or SUF (Stefaniak et al. 2006), and the rate of dissolution of the multiconstituent arc-furnace particles was greater than that of the single-constituent beryllium oxide powder. The authors speculated that copper in the particles rapidly dissolves, exposing the small inclusions of beryllium oxide, which have higher SSA and therefore dissolve at a higher rate. The higher rate of dissolution of beryllium in the copper-beryllium alloy could increase the risk of CBD in workers exposed to this type of aerosol by making beryllium oxide more biologically available. Conversely, CBD risk could be less because the increased solubility of multiconstituent beryllium particles would decrease the residence time in the lungs.

Because an oxide layer may form on beryllium-metal surfaces on exposure to the atmosphere (Mueller and Adolphson 1979), Harmsen et al. (1984) have suggested that dissolution of small amounts of poorly soluble beryllium compounds in the lungs might be sufficient to allow persistent low-level beryllium presentation to the immune system. It is clear from the available studies that more efforts are required to evaluate the role of intrapulmonary dissolution in beryllium-induced immune system stimulation and development of CBD.

CONCLUSIONS AND RECOMMENDATIONS

Beryllium concentrations in a workplace vary substantially according to the production process and differ from location to location within a factory at any given time. Most of the available information on exposure comes from settings in which beryllium is mined, processed, or manufactured into beryllium-containing products and materials. The Air Force uses beryllium-alloy products in its aerospace applications, so its exposure scenarios are likely to be different from those in manufacturing and production settings. Maintenance and mechanical workers should be carefully considered because those tasks have been identified in other settings as having high exposure to beryllium particles.

The committee found that several exposure measures probably affect the exposure-response relationship between beryllium and the development of CBD. Development of CBD is associated with inhalation of relatively insoluble beryllium particles. At the cellular level, inhaled beryllium metal must be solubilized for cell-mediated immune reactions to occur. Many factors can influence the presentation of soluble beryllium to the immune system. Those factors include the amount of inhaled material and the physicochemical characteristics (such as composition, structure, size, and surface area) that affect solubility. In addition, the aerodynamic size of the aerosol will affect the amount and site of deposition in the respiratory tract. Recent research indicates that surface area and dissolution rate in the lungs also contribute to the rate of release of beryllium ions.

The epidemiologic literature suggests that developing BeS or CBD is process-related (see Chapter 3). It is not possible, however, to conclude confidently from those studies that specific types of beryllium are more toxic than others. Further epidemiologic study might be able to answer that question, but epidemiology is often a blunt analytic tool. Detecting differences in beryllium toxicity as a function of particle characteristics requires exposure of large numbers of people to various types of beryllium for an appropriate duration to be at risk for developing disease. Such cohorts have not yet been identified. Until there is strong evidence that some forms of beryllium are more or less toxic than others, it is prudent from a safety and health perspective to treat them equally.

More research is needed on the aerosol characteristics of detectable beryllium, including particle size distribution, surface area, and chemical composition.

Research is also needed to understand the extent of skin exposure to beryllium and the associated risks, if any. The effectiveness of personal protection equipment and other workplace controls to reduce skin exposure should be investigated.

3

Epidemiologic and Clinical Studies of Beryllium Sensitization and Chronic Beryllium Disease

It is well established that beryllium causes sensitization (beryllium sensitization, BeS) and chronic beryllium disease (CBD). This chapter assesses the risk of those conditions posed by occupational exposure to beryllium. We first review the epidemiologic literature on BeS and CBD and then present the current clinical description of CBD with diagnostic, testing, and management approaches. Chapter 4 presents what is known about the pathogenesis and mode of action of CBD, genetic factors that confer susceptibility to it, and animal models for studying CBD.

EPIDEMIOLOGIC LITERATURE

Exposure to airborne beryllium-containing particles can cause two distinct types of pulmonary disease: a pneumonitis referred to as acute beryllium disease and a chronic granulomatous disease called CBD. Acute beryllium disease, first reported in the 1940s, was observed in beryllium workers and was characterized by the onset of severe respiratory symptoms, usually over several weeks. Chest radiographic descriptions were those of initial diffuse haziness followed by lung infiltrates and nodules. Most patients recovered over several months with appropriate treatment and removal from exposure, but the condition recurred on renewed exposure (Van Ordstrand et al. 1945). Autopsy results in seven fatal cases showed pulmonary edema, mononuclear cell exudate, fibrosis, nodules, and one case of well-defined granulomas (Dutra 1948). The incidence of acute beryllium disease decreased after respiratory exposure to beryllium was controlled (Van Ordstrand et al. 1945). The mechanism may be a toxic pneumonitis, although immune or hypersensitivity responses are also possible. Acute beryllium disease has been reported only rarely in the last several decades.

CBD, however, despite substantial reductions in beryllium respiratory exposures, continues to occur in exposed workers. The pathogenesis of CBD involves a lymphocyte-mediated immune response (delayed hypersensitivity) to beryllium that leads to noncaseating granulomatous lesions. CBD affects primarily the lungs, although granulomas can occur in other organs, such as skin, liver, and spleen. BeS precedes the development of CBD and since the late 1980s has been detected by in vitro challenge of lymphocytes with beryllium salts in the beryllium lymphocyte proliferation test (BeLPT). In the older literature, patients with CBD typically presented with respiratory symptoms, fatigue, and chest-radiographic and lung-function abnormalities. Since the BeLPT has been available, screening of workers with it has enabled diagnosis of CBD often when they have minimal or no symptoms. That has shifted the clinical spectrum of CBD toward less severe cases. The recent epidemiologic literature on BeS and CBD and their clinical presentation, diagnosis, and management are reviewed below.

In the United States, acute beryllium disease was first reported in the early 1940s by Van Ordstrand et al. (1943); the first reports of CBD were by Hardy and Tabershaw (1946). Cases were observed in industrial plants that were refining and manufacturing beryllium metal and beryllium alloys and in plants manufacturing fluorescent light bulbs. By 1948, the known cases totaled more than 400, and

the basic clinical features of the disease were understood. It was established that the risk of disease among beryllium workers was variable and generally rose with the intensity of airborne exposure (Machle et al. 1948; see Chapter 2 for more information). From the late 1940s into the 1960s, clusters of CBD cases were identified around beryllium refineries in Ohio and Pennsylvania, and outbreaks in family members of beryllium-factory workers were presumably from exposure to contaminated clothing (Hardy 1980). Although there was a relationship between the air concentration of beryllium and the risk of CBD in areas close to the factories, the disease rates outside the plants were higher than expected and not very different from the rate of CBD in the workforce (Eisenbud et al. 1949; Lieben and Metzner 1959).

The prevalence of CBD in workers exposed during the 1940s and 1950s has been estimated at 1-10% (Eisenbud and Lisson 1983) although there is considerable uncertainty because most of the studies in that era did not use well-defined cohorts, modern diagnostic methods, or have adequate followup.

Sterner and Eisenbud (1951) first proposed an immunologic mechanism of CBD in 1951. Their evidence was largely circumstantial, but their inference was correct. They based their hypothesis on several pieces of evidence: the highly variable incidence in different groups of workers, the surprising occurrence in neighborhoods whose exposure appeared to be low, the sometimes rapid onset of disease after exposure, and the failure to observe an association between the amount of beryllium in lung autopsy specimens and the extent of lung damage.

From the 1940s through the 1960s, the Atomic Energy Commission (AEC) was the primary user of beryllium in the U.S. economy. In 1949, AEC's occupational hygienists recommended an air standard of 2 $\mu g/m^3$ as an 8-h time-weighted average and a 30-min peak standard of 25 $\mu g/m^3$ (Eisenbud 1982). Before the widespread application of the BeLPT, it appeared that strict adherence to those standards might adequately protect workers from CBD. However, it is now clear that CBD can occur in factories that have beryllium aerosol concentrations consistently below 2 $\mu g/m^3$ (Kreiss et al. 2007).

The development of the BeLPT changed case-finding tools used in CBD epidemiologic studies from chest radiography and spirometry to the identification of BeS with a blood test followed up with clinical examination. That change made it difficult to compare findings from the clinical and epidemiologic literature before and after BeLPT development. With reductions in exposure in many beryllium workplaces, the widespread use of the BeLPT has meant that in recent years CBD has often been diagnosed when there has been less severe evidence of disease. There appears to be a consensus in the field that a case series of CBD identified in exposed workers with the BeLPT and confirmed with biopsies provides more specificity in diagnosis than such tools as chest radiography and spirometry. In its review of the epidemiologic evidence, the committee decided to focus primarily on the epidemiologic studies of CBD that included the use of the BeLPT. The committee took into account the results of the older epidemiologic studies, clinical studies, and case series that described clinically diagnosed CBD in the pre-BeLPT era to inform other sections of this chapter (see sections on "Presentation and Diagnosis of and Testing for Chronic Beryllium Disease" and "Progression and Management of Chronic Beryllium Disease").

In a recent review, Kreiss et al. (2007) summarized 12 studies (with overlapping populations) in which CBD prevalence was assessed cross-sectionally and ranged from 0.1% to nearly 8% (Table 3-1 is a modification of a table of Kreiss et al.). The higher prevalence of BeS and CBD in the facilities studied by Kreiss et al. (1989, 1997), Henneberger et al. (2001), Newman et al. (2001), and Rosenman et al. (2005) is at least partly explained by higher airborne concentrations of beryllium in those facilities. The newer epidemiologic studies have benefited from the ability to detect BeS with the BeLPT, and their results indicate that in general the prevalence of BeS is higher than that of clinically confirmed CBD although the difference varies widely. The differing ratios of BeS to CBD among studies are probably affected by the extent of followup of former workers, the time elapsed since initial exposure, and the physical form and intensity of exposure.

It is difficult to estimate the "background" risk of CBD. Although there is nonoccupational exposure to beryllium in soils, air, food, and water, the committee knows of no studies that have attempted to identify cases from "natural" sources. There have been case reports of CBD in people with incidental or inconsequential exposure to beryllium, but such reports are of little use in estimating

background risk. It is also likely that many cases of CBD are mistakenly diagnosed as sarcoidosis; without a known source of exposure and lacking a BeLPT, there is no way to distinguish these CBD cases from sarcoidosis.

TABLE 3-1 Summary of Recent Epidemiologic Studies of Chronic Beryllium Disease

Reference	Study Type	Prevalence		Exposure-Response Relationship?[a]	Comments
		BeS	CBD		
Mining and extraction					
Deubner et al. 2001a	Cross-sectional	4.0%	1.3%	No	
Beryllium-metal processing, alloy production					
Kreiss et al. 1997	Cross-sectional	9.4%	4.6%	No	
Newman et al. 2001	Longitudinal	9.4%	5.5%	No	
Kelleher et al. 2001	Case-control	N/A	N/A	Yes	
Rosenman et al. 2005	Cross-sectional	14.6%	7.6%	No	
Beryllia ceramics					
Kreiss et al. 1993a	Cross-sectional	1.6%	1.8%	No	
Kreiss et al. 1996	Cross-sectional	5.9%	4.4%	Yes	
Henneberger et al. 2001	Cross-sectional	9.9%	5.3%	Yes	
Cummings et al. 2007	Longitudinal	N/A	N/A	Yes	
Beryllium-copper alloy processing, distribution					
Schuler et al. 2005	Cross-sectional	6.5%	3.9%	No	
Stanton et al. 2006	Cross-sectional	1.1%	1.1%	No	Workers in three distribution centers
Nuclear-weapons industry					
Rocky Flats nuclear-weapons facility					
Kreiss et al. 1989	Cross-sectional	11.8%	7.8%	No	Production, research and development machinists only
Kreiss et al. 1993b	Cross-sectional	1.9%	1.7%	No	Stratified random sample with probable beryllium exposure
Stange et al. 1996b	Longitudinal	2.4%	0.7%	No	Current, former workers
Stange et al. 2001	Longitudinal	4.5%	1.6%	No	Current, former workers (including workers in Stange et al. 1996b)
Sackett et al. 2004	Cross-sectional	0.8%	0.1%	No	Decontamination, decommissioning workers only
Viet et al. 2000	Case-control	N/A	N/A	Yes	Current, former workers
Hanford Nuclear Reservation, Oak Ridge Reservation, Savannah River site					
Welch et al. 2004	Cross-sectional	1.4%	0.1%	No	Construction-trade workers

[a]No, no evidence of exposure-response relationship provided in paper; Yes, evidence of increased prevalence or risk with increasing exposure.
Source: Adapted from Kreiss et al. 2007. Adapted table printed with permission; copyright 2007, *Annual Review of Public Health*.

Natural History of Beryllium Lung Disease

The committee found it useful to summarize the main pathologic processes that lead to CBD in a simplified schematic (Figure 3-1). The steps in the scheme may be described as follows:

Step 1—Sensitization: It is presumed that sensitization precedes CBD. It is unclear whether BeS can resolve or go away, inasmuch as the reversion of an abnormal BeLPT to normal could occur for a number of reasons, such as recruitment of beryllium-responsive cells to the lung, variability in the BeLPT, or development of immune tolerance. In general, immune responses and the ability to detect them vary over time.

A beryllium dose to the immune system is necessary for sensitization, but the shape of the dose-response curve (represented by curve 1 in the figure) is not known. There are probably different curves for different subpopulations distinguished by genotypes and possibly other host factors. Some fraction of the population may be incapable of sensitization no matter what their beryllium dose is, but this is not known. The time during which exposure is relevant to the risk of sensitization also is not known. Studies suggest that the incubation period for sensitization can be as short as a few months of exposure (Kelleher et al. 2001; Cummings et al. 2007; Donovan et al. 2007). The exposure period before ascertainment of sensitization was found by Madl et al. (2007) to be highly variable, ranging from 0.2 to 22 years with a median of 2.0 years. Finally, it is likely that there are different dose-response curves depending on the physicochemical form of beryllium, particularly with respect to solubility and particle size; however, the data are sparse, and it is not now possible to estimate separate curves for different types of beryllium.

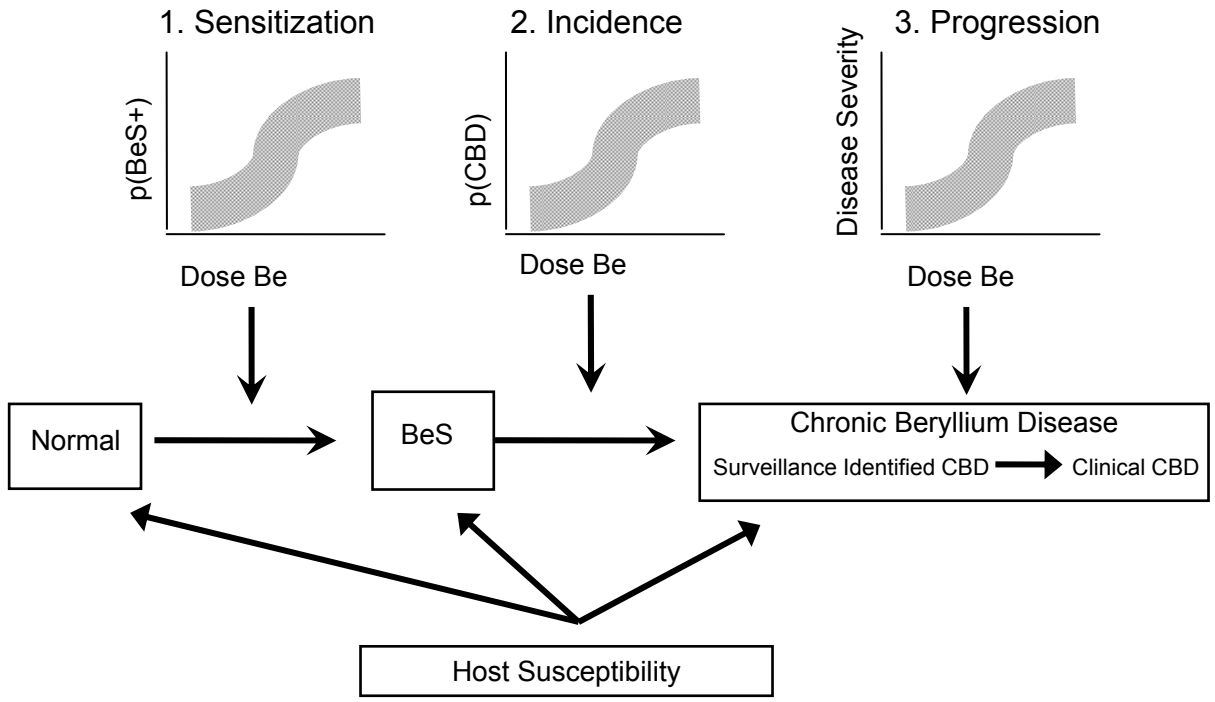

FIGURE 3-1 Simplified schematic of natural history of beryllium sensitization (BeS) and chronic beryllium disease (CBD). Some time after initial exposure, normal workers may become sensitized through exposure-response process represented by curve 1. Once they are sensitized, further exposure may lead to CBD (curve 2). Progression of CBD may also occur; third exposure-response relationship contributes to this process (curve 3). Host susceptibility is probably important at all three steps. p(BeS+) = probability of BeS, p(CBD) = probability of CBD.

Step 2—Incidence: The likelihood of developing CBD depends on factors such as time, beryllium dose (as represented in the figure by curve 2), and host factors. As with sensitization, the shape of the dose-response curve for CBD incidence (the epidemiologic term for first onset of disease) is not known. It is likely to be different from the relationship in the first step (curve 1) and probably also has genetic determinants that result in different dose-response relationships (or beryllium potencies) in different subpopulations. The genetic polymorphisms that act in this stage may differ from the ones that act in the first stage (see Chapter 4).

Step 3—Progression: Some, perhaps many, of the surveillance-identified cases of CBD will not have any impairment in function, at least on initial diagnosis. (The condition is sometimes called "subclinical CBD". However, the committee considers it part of the spectrum of CBD, which can range from disease with no apparent functional impairment to severe lung disease. Some cases of surveillance-identified CBD can progress to more severe disease, as discussed later.) Again, some dose-response curve probably underlies the progression, but little is known about it; the relevant period, an appropriate exposure metric, and relative potencies of different physicochemical forms are all unknown.

The recent literature on BeS and CBD in different sectors of the beryllium industry is summarized briefly below. The division into sectors may be useful because it corresponds roughly to the physicochemical forms of beryllium to which workers are exposed. There are a number of methodologic issues and differences between the epidemiologic studies, including study design, number of study participants, how exposure was quantified, diversity of physicochemical form of beryllium, genetic susceptibility to CBD, and the healthy-worker effect. The section "Challenges in Interpreting the Epidemiologic Literature on Beryllium Disease" later in this chapter elaborates on some of the challenges to understanding CBD risk and how they limit the interpretability of the epidemiologic studies.

Beryllium Mining and Extraction

There is some information on the risk of CBD in workers in beryllium mining and extraction. In the United States, beryllium ore is mined in a single facility in Utah; substantial mineral resources also exist in China, Russia, and elsewhere. The U.S. facility has been studied twice: by Rom et al. (1983), who reported on worker-health surveys in 1979 and 1982, and more recently by Deubner et al. (2001a). The Rom et al. study used an early version of the BeLPT, and its results are difficult to interpret. The Deubner et al. study appears to provide a more reliable assessment of the risk in mining and extraction.

Bertrandite ore (containing an average of 0.23% beryllium) is mined at the Utah facility, and an extraction mill at the same site produces beryllium hydroxide, which is shipped elsewhere to be made into beryllium oxide ceramics and beryllium metal. The same facility produces beryllium hydroxide from beryl ore (3.6-5.0% beryllium) that is mined abroad. A medical-surveillance study in 1996 included the BeLPT (Deubner et al. 2001a). Of the 87 workers in the facility, 75 (86%) were tested; 12 refused. The single worker found to have CBD had had substantial exposure to beryllium in another facility. Three beryllium-sensitized workers had worked only in the facility under study. It is not possible from the data given to conclude that there is no risk in mining and extraction. The paper does not permit an analysis that separates mine workers from mill workers, so it is not possible to estimate the prevalence or risk of sensitization separately for the two activities—mining, in which exposure is exclusively to highly dilute ores, and extraction, in which beryllium salts are present. It appears that there may be a lower risk of sensitization in mining and extraction than in other phases of production, but confidence in this finding is limited by the small numbers, limited participation, and inability to separate exposures in mining and in extraction.

Beryllium-Metal Processing and Alloy Production

The beryllium-metal processing and alloy-production facilities have provided important data on risks of BeS and CBD and the relationships between the two (Kreiss et al. 1997; Kelleher et al. 2001; Newman et al. 2001; Rosenman et al. 2005; Madl et al. 2007). The relevant studies involved cross-sectional screening of a working population, and each found both BeS and CBD (Table 3-1).

Rosenman et al. (2005) studied a large group (1,351) of former workers of a beryllium-processing plant more than 25 years after the end of exposure. Exposure reconstruction was used to assign beryllium-exposure histories to all cohort members, who were offered medical screening, including BeLPT. Those with BeS were invited to a further workup, including bronchoalveolar lavage for BeLPT testing of lavage fluid and histologic evaluation for granulomas. The overall prevalence of BeS (6.9%) and prevalence of definite or probable CBD (7.6%) were higher than in other studies although historical exposure at this plant was also higher than more recent exposure in other plants that were studied. The authors compared workers with BeS and CBD with nonsensitized workers with respect to several exposure metrics and found only limited evidence of an exposure-response relationship. The findings were weakened, however, by substantial losses to followup, refusals to participate in medical monitoring, and limited exposure data. The exposure-response findings are probably biased by the healthy-worker effect and exposure misclassification.

The study by Newman et al. (2001) is valuable because the same population was studied in a later case-control analysis (Kelleher et al. 2001) to investigate exposure-risk relationships that go beyond the prevalence data presented in most studies. The two studies were conducted in a beryllium-metal machining facility that experienced an index CBD case in 1995. The plant opened in 1969, and extensive environmental measurements were taken throughout the plant's history. Beginning in 1995, BeLPT screening of all workers was conducted, with retesting 2 years later. All 235 eligible workers were tested in 1995-1997, and 15 (6.4%) were beryllium-sensitized. Of the 15 sensitized workers, 12 completed clinical evaluations, and nine were found to have CBD. The onset of sensitization was sometimes very short—3 months or less in four of the 15.

To investigate exposure-response relationships, seven workers with BeS and 13 with CBD were compared with 206 at-risk workers who had neither condition in a case-control analysis (Kelleher et al. 2001). Exposure of cases and controls was assessed by using personal exposure data that had been gathered with a size-selective impactor in the breathing zone. Cumulative and average lifetime exposures were calculated for particles of two sizes: less than 6 μm and less than 1 μm. There was evidence that case subjects were more highly exposed than controls in terms of both total exposure and in the two size ranges. For example, cumulative exposure to particles smaller than 1 μm was associated with the prevalence of BeS or CBD when prevalence was compared in three exposure groups. In comparison with those who had low cumulative exposure (less than 0.09 $\mu g/m^3$), the odds ratio (OR) in those with medium exposure (0.09-1.87 $\mu g/m^3$) was 1.85, and the OR in those with high exposure (over 1.87 $\mu g/m^3$) was 2.46. Confidence intervals were rather wide because of the small numbers of cases, but a trend was clear.

More recently, Madl et al. (2007) evaluated exposure-response relationships between beryllium exposure and BeS and CBD in workers in the same metal-machining plant that was studied by Kelleher et al. (2001). A number of indexes of beryllium exposure were estimated for each of the nine workers who were identified as beryllium-sensitized and 18 as having CBD since 1995. Many air sampling measurements were available for these workers, and five exposure metrics were estimated for each of the 27 cases; each metric represented a slightly different assumption about which aspect of an exposure profile is most important in predicting risk. For example, three of the five metrics attempted to estimate the time-weighted-average exposure in the year of highest exposure of each worker. Another approximated an overall average lifetime exposure of each worker. Unlike Kelleher et al., Madl et al. did not include a formal epidemiologic study design that might have permitted investigation of exposure-response relationships. Probably the most straightforward approach would have been a nested case-control study, drawing controls from the at-risk population of the plant and using incidence-density sampling. Without a comparison population, it is not possible to use the results to investigate the

possibility of a threshold of exposure below which there is no risk, nor can one estimate the risk at different exposures. The results do provide one important insight that is not limited by the lack of a comparison population: BeS and CBD developed in some workers after air exposure that was below 0.2 $\mu g/m^3$. More detailed predictions of the distribution of exposure magnitudes leading to disease cannot be supported by the data, given the small number of workers with BeS and CBD and the lack of a comparison population.

Other studies have suggested that BeS or CDB can occur at exposure below 0.2 $\mu g/m^3$. Kelleher et al. (2001) reported that eight of 20 workers with BeS or CBD in a beryllium-machining facility had individual lifetime-weighted (LTW) exposure of less than 0.2 $\mu g/m^3$, whereas none of the workers with LTW exposure below 0.02 $\mu g/m^3$ had BeS or CBD. In a study of beryllium exposure in an aluminum smelter (see description below), Taiwo et al. (2008) found two workers with CBD whose mean beryllium exposure was 0.16 and 0.04 $\mu g/m^3$.

In summary, the literature on beryllium-metal processing and alloy production provide many of the available data on BeS and CBD.

Beryllium Oxide Ceramics

Beryllium oxide–ceramics production workers in two facilities have been studied: one that produced ceramics until 1975 (Kreiss et al. 1993a), and a second that still produces ceramics (Kreiss et al. 1996; Henneberger et al. 2001; Cummings et al. 2007). Those studies are among the best sources of evidence of the risk of BeS after low exposure.

The plant that still produces ceramics has monitored workers closely for the onset of sensitization (and for CBD in those who become sensitized) over about 10 years. The facility has also engaged in increasingly elaborate control procedures in an attempt to eliminate the risk of sensitization. BeS screening with the BeLPT was first conducted in 1992, when eight (5.9%) of 136 screened workers were found to be sensitized. Six of the eight had CBD as evidenced by granulomas in biopsied lung tissue. The highest risk was in machining, which had higher average mass concentrations of beryllium in air than other jobs. At the initial 1992 screening, the prevalence of BeS was higher in machinists (14.3%) than in all other workers (1.2%). After the survey, the company undertook engineering controls to reduce airborne exposures over the period 1993-1996. Employment increased in 1996, and a second BeLPT screening was conducted in 1998. A detailed assessment of airborne exposures was carried out at the same time. Overall, 15 (9.9%) of 151 screened workers had BeS in 1998.

Those results are best understood by looking separately at two groups: long-term workers who had been employed before the first screening in 1992 and short-term workers who were hired after it. The short-term workers had experienced only recent exposure to beryllium, and their exposure-risk experience was less likely to have been biased by loss to followup than that of the long-term workers. But the prevalence of BeS was similar in the two groups: 10.4% in 77 long-term workers and 9.5% in 74 short-term workers. The investigators observed that short-term workers with "low" mean exposure (0.05-0.28 $\mu g/m^3$) had a lower prevalence of sensitization (5%) than those with higher exposure (0.29-4.4 $\mu g/m^3$; 14%). That fairly large difference in prevalence was based on very small numbers: 39 workers with low exposure and 35 with high exposure.

Concluding that additional ventilation controls had not reduced the prevalence of sensitization, the company embarked on a second, much more elaborate control strategy, including respiratory protection, reduction in skin contact, stricter control of airborne exposure, and improved housekeeping practices. From 2000 on, as new workers were hired, they received baseline sensitization tests so that the incidence of sensitization could be quantified prospectively. Cummings et al. (2007) assessed the effectiveness of the post-2000 exposure-control program by comparing the incidence of sensitization in workers hired from 2000 to 2004 with the incidence in those hired from 1993 to 1998. From 2000 to 2004, 126 workers were hired, and most contributed a baseline result and at least one postbaseline test result. The results were compared with those of the 69 workers tested in the 1998 survey. The two groups

of workers were of similar mean age (37 and 35 years, respectively), and both had mean tenures of 16 months. The incidence of BeS in those hired in 2000-2004 was 0.7 worker per 1,000 person-months, and the incidence in the group hired earlier was 5.6 workers per 1,000 person-months. Although that is a large difference, it was based on very small numbers: one worker in 1,480 person-months and six workers in 1,081 person-months, respectively.

It appears from the Cummings et al. paper that an extensive control program—including scrupulous attention to skin contact, inhalation exposure, and dust control throughout the facility—was effective in reducing (but not eliminating) the risk of sensitization. Comparison of the first (1992) and second (1998) surveys suggested that engineering control of airborne exposure alone was not sufficient to eliminate the risk of sensitization (Henneberger et al. 2001).

Taiwo et al. (2008) recently reported findings from a voluntary beryllium-surveillance program for aluminum-smelter workers with low beryllium exposure (median concentration, 0.05 $\mu g/m^3$). BeS was found in two (0.27%) of 734) of the workers on the basis of two abnormal BeLPT results. On further evaluation, probable CBD was diagnosed in the two workers; attempts to obtain lung tissue with bronchoscopy were unsuccessful. Although it was a low prevalence, probable CBD was detected in a group of workers in whom it previously was not suspected and who do not routinely undergo surveillance.

In summary, the experience with BeS and CBD in the beryllium oxide industry has been particularly important in providing evidence of the effectiveness of exposure-control programs.

Copper-Beryllium–Alloy Processing and Distribution

Case reports document the occurrence of CBD in workers exposed to 2% beryllium-copper alloy (Balkissoon and Newman 1999), but they had experienced substantial exposure through grinding, heating, and cutting operations. Two studies of beryllium-copper–alloy processing and distribution facilities have provided data on risks of BeS and CBD and the relationship between them (Schuler et al. 2005; Stanton et al. 2006). A study of beryllium-copper distribution-center workers provided some information on the risk to those with more modest exposure (Stanton et al. 2006). Some processing of beryllium-copper strip and rod took place at the facilities, including sawing, heat treating, welding, and slitting; but dust- and fume-generating activities should have been lower than in beryllium-manufacturing facilities. Exposure-monitoring data confirmed the generally low airborne exposures: the median concentration of 393 full-shift personal samples was 0.03 $\mu g/m^3$, 97% of the values were less than 0.2 $\mu g/m^3$, and no samples exceeded 2 $\mu g/m^3$. Of the 100 current workers invited to participate in a cross-sectional health survey, 88 agreed; one was found to be sensitized to beryllium and, after clinical examination, found to have CBD. That worker had spent 22 years in a production-support job as a shipper and receiver.

That case and others (Kreiss et al. 1996; Hennenberger et al. 2001; Schuler et al. 2005) indicate that CBD can occur in workers exposed at below an air concentration of 2 $\mu g/m^3$.

Nuclear-Weapons Production and Cleanup

A series of studies have investigated BeS and CBD in workers in nuclear-weapons production facilities, including the cleanup of those plants (Kreiss et al. 1989, 1993b; Stange et al. 1996b, 2001; Viet et al. 2000; Sackett et al. 2004; Welch et al. 2004). The U.S. Department of Energy conducts health surveillance of workers potentially exposed to beryllium at its facilities, and the surveillance data form the basis of this set of studies. Results of surveillance at the Rocky Flats nuclear-weapons facility near Denver have been presented (Kreiss et al. 1989, 1993b; Stange et al. 1996b, 2001, 2004; Viet et al. 2000; Sackett et al. 2004). Welch et al. (2004) studied construction workers at three other facilities: in Hanford, Washington; Oak Ridge, Tennessee; and Savannah River, South Carolina. Those studies were all cross-sectional and based on health surveys of various worker cohorts. They share many of the limitations of

other beryllium epidemiologic studies, including less than 100% participation of the target population, loss to followup, and inadequate exposure data or inadequate ability to link exposure data to specific study participants. Despite their limitations, they provide useful data on risks in a fairly large and diverse group of workers in the nuclear industry.

BeS and CBD were reported in each of the studies in workers who handled beryllium metal and alloy and in those who performed various tasks involved in cleaning up former weapons facilities where beryllium was handled. Cross-sectional prevalence of BeS was 0.8-11.8% and of CBD 0.1-7.8%.

Viet et al. (2000) used the surveillance and exposure monitoring data from Rocky Flats to investigate exposure-risk relationships. They conducted a case-control sampling of the surveyed cohort, choosing as case subjects all those who had been identified with BeS or had clinically diagnosed CBD. Controls were chosen by 1:1 sampling and matching to cases on age, sex, race, and smoking. There were 74 workers with BeS without evidence of CBD and 50 workers with CBD. For each case and control, a lifetime beryllium-exposure history was constructed by using job-history information combined with estimates of exposure in each job based on fixed-area samples. Although the number of air samples was large, the samples were taken not in the workers' breathing zones but rather at fixed locations throughout the workplace. One would expect some exposure misclassification from this monitoring system. The resulting error may have reduced the strength of the association between exposure and risk.

Cumulative and average exposure estimates were fitted to case-control status in logistic-regression models. There was evidence of increasing risk of CBD with increasing beryllium exposure, particularly cumulative exposure. The evidence of an association with BeS was not as strong. Although the cross-sectional nature of the study limited risk prediction in important ways, the authors estimated that there was a 0.5% risk of CBD at the current standard of 2 $\mu g/m^3$.

Longitudinal Studies of Progression of Beryllium Sensitization

Few studies have attempted to investigate the progression of BeS to CBD. They have been small and varied in design, exposure setting, length of followup, and diagnostic evaluation. In one of the earliest clinical studies to use the BeLPT, Rom et al. (1983) reported that 13 of 82 beryllium-mining and -milling workers had BeS. None of the sensitized workers developed CBD over the following 3 years, and some showed possible reversal of sensitization. However, the initial diagnosis of BeS was based on only one positive result of an early version of the BeLPT, so it is difficult to interpret (see discussion of the BeLPT later in this chapter).

Newman et al. (2005) followed a cohort of 55 patients with BeS at 2-year intervals for a mean followup of 4.8 years to determine progression to CBD. BeS was defined on the basis of two abnormal BeLPTs and no evidence of pathologic changes (granulomas or mononuclear cell infiltrates) on transbronchial biopsy. CBD was defined on the basis of evidence of BeS and pathologic changes. Of the 55 patients with BeS, 17 (31%) developed CBD within an average followup period of 3.8 years. Work as a machinist, a job with higher exposure to airborne beryllium, was associated with progression from BeS to CBD. Lung function was normal and similar in both groups at baseline, and only limited followup data were provided. The authors estimated that BeS progresses to CBD at a rate of 6-8% per year after diagnosis. However, it is possible that some people had pathologic changes on their initial evaluation that were missed and thus had not actually progressed. It appears that there were no differences in baseline or followup lung function between those who had BeS and those who had a diagnosis of CBD, but additional followup of both groups is needed. Of the 17 who developed CBD, 11 had further followup, some of whom showed lung-function declines, but only limited data were presented on this group. One person with CBD was treated with steroids. Longer followup of this group and of others with BeS is needed to determine the natural history and prognosis of BeS.

Risk Posed by Low-Level Environmental Exposure

CBD has occurred in people thought to have trivial, unrecognized, or brief exposure to beryllium. Examples include secretaries, security guards, end-product inspectors, and workers hired years after beryllium operations ceased (Kreiss et al. 1993a,b, 1996; Eisenbud and Lisson 1983). Family members of beryllium workers have developed CBD thought to have occurred from contact with contaminated clothing (Lieben and Metzner 1959; Eisenbud and Lisson 1983; Newman and Kreiss 1992). Although in some of those cases it is not possible to rule out occupational exposure, the overall picture is that people can develop CBD from beryllium exposures that would generally be considered incidental.

Cases of CBD have also been reported in residents of communities that surround beryllium-manufacturing facilities. Data are not available on the exposure encountered in those situations, and it is difficult to rule out occupational exposure in some of the cases (Lieben and Metzner 1959; Dattoli et al. 1964; Lieben and Williams 1969; Newman and Kreiss 1992).

Maier et al. (2008) recently reported eight cases of CBD diagnosed in 1972-2002 in a community surrounding a beryllium-manufacturing plant in Reading, Pennsylvania. The authors attributed the cases of CBD to past community exposure to beryllium, given that workplace exposure was excluded to the extent possible. Average exposure to beryllium was estimated to be 0.015-0.028 $\mu g/m^3$ with possible peak exposure greater than 0.35 $\mu g/m^3$ on the basis of historical beryllium air sampling in 1958. In addition to constituting further evidence that CBD can occur after relatively low exposure, those cases highlight how easily the diagnosis of CBD can be missed, especially if the patient is not aware of past beryllium exposure, as is not uncommon (Redlich and Welch 2008). Because exposure probably occurred 20 years or more before diagnosis, the cases also highlight the fact that CBD can present many years after exposure ends. That long latency can hinder recognition and supports the rationale for continued surveillance of workers at risk for CBD.

Risk Posed by Skin Exposure

Research and prevention have focused largely on airborne exposure. However, BeS and CBD have persisted despite reductions in respiratory exposure, and a possible role of skin exposure has been suggested (Day et al. 2007; Kreiss et al. 2007).

Decades ago, workers developed contact dermatitis from skin exposure to soluble beryllium salts, which was confirmed with beryllium skin-patch testing (Curtis 1951). Patch testing that used beryllium salts (such as beryllium fluoride, beryllium sulfate, and beryllium chloride) was developed as a diagnostic test for CBD but was discontinued because of concerns that such testing itself could cause contact dermatitis or BeS or worsen CBD (Curtis 1951, 1959). Patch testing with elemental beryllium and beryllium oxide powder yielded no positive reactions.

The question of whether low-solubility particulate forms of beryllium metal, oxides, and alloys can penetrate human skin has been raised (see Chapter 2) and has yet to be answered. An increased risk of CBD has been reported in workers who have skin lesions, which might increase uptake of beryllium (Johnson et al. 2001; Schuler et al. 2005). As noted earlier, particulate forms of beryllium, like such other particles as titanium dioxide and polystyrene latex spheres, may be able to penetrate normal human skin (Tan et al. 1996; Tinkle et al. 2003). BeS has also been produced in mice by skin exposure to beryllium oxide particles (Tinkle et al. 2003).

A few studies of beryllium-exposed workers have begun to focus on measuring and preventing surface and skin exposures. Cummings et al. (2007) described a comprehensive prevention program in one beryllium oxide ceramics plant targeted at respiratory and skin protection (details were provided earlier in this chapter). The program included use of personal protective equipment (PPE) and administrative changes geared to reducing beryllium in the air, on all work surfaces, and on skin. After implementation of the program, the rate of BeS was reduced. Long-term followup of the cohort is needed to determine whether the risk of BeS remains low.

A recent exposure assessment at a copper-beryllium alloy facility documented beryllium contamination of work surfaces and gloves and exposure of skin of the neck and face and under gloves (Day et al. 2007). Air beryllium concentrations correlated strongly with the degree of contamination of work surfaces, and concentrations on work surfaces, gloves, and skin also correlated.

It has been suggested that skin exposure to other occupational and environmental sensitizers, such as isocyanates, may lead to systemic sensitization that can progress to lung disease if there is also respiratory exposure (Bello et al. 2006; Redlich and Herrick 2008).

The hypothesis that skin exposure may lead to sensitization, if correct, has several implications for pathogenesis, risk factors, and prevention. For example, some forms of exposure may make beryllium more bioavailable to the skin (soluble metals and liquids) and others more bioavailable to the lung (respirable particles and vapors); the hazard associated with beryllium may depend on its route of entry. If skin exposure can lead to sensitization, regulatory standards based on air concentrations, even if very low, may not prevent sensitization.

Challenges in Interpreting the Epidemiologic Literature on Beryllium Disease

In reviewing the epidemiologic literature on BeS and CBD, the committee often found limitations in the current evidence base that made it difficult to respond confidently to a number of the questions in the committee's charge. These have been noted in discussing specific epidemiologic studies, and this section summarizes some of the methodologic challenges found in the beryllium-epidemiology literature, such as issues with study design, exposure assessment, selection bias, specific characteristics of CBD and BeS, and size of the study population.

Study Design

Definitive diagnosis of CBD often requires an invasive procedure to obtain lung tissue. As a result, there is little information on the prevalence of pulmonary granulomas and other signs of CBD in populations that have not been found to have BeS. Testing for BeS is also invasive (although much less so than CBD diagnosis) because it requires at least one blood sample. The invasiveness of the procedures imposes a fundamental limitation on the study of CBD: most studies are cross-sectional, and their study populations are self-selected. BeS or CBD identified in cross-sectional studies are prevalent outcomes; we do not know the date of onset or incidence unless the population is subject to frequent repeated screening and the time of onset of sensitization can be tied to a particular interscreening interval. Typically, workers object to frequent blood drawing, so the intervals may be several years, and participation decreases with time. The BeLPT is an expensive test, and this also limits how frequently it is administered.

Quantification of Exposure

Exposure measurement for beryllium studies is challenging (see Chapter 2) and imposes serious limitations on the utility of the available literature. The standard methods for monitoring air in beryllium facilities have changed, and the change introduces uncertainty into estimates of lifetime exposures. Evidence suggests that there is risk of disease at concentrations below 0.2 $\mu g/m^3$.

Many of the available historical exposure data were collected at fixed locations and not in the breathing zones of workers (see especially the case-control study of Viet et al. [2000]). This practice probably introduced additional exposure misclassification into exposure-risk estimates, particularly with regard to brief peaks of exposure.

There is also some indication that the skin may be a route of exposure, and quantification of dermal exposure is difficult and rarely carried out systematically. Beryllium-containing particles that are

transferred by the skin or clothing to the breathing zone or the mucous membranes of the respiratory system will not be captured or represented by breathing-zone air sampling. Thus, there are no studies that permit investigation of quantitative exposure-risk relationships in which workers' exposures by both the respiratory and dermal routes have been jointly assessed.

Studying an Immune-Mediated Disease

As described in Chapter 4, there is strong evidence that susceptibility to beryllium's effects on the lungs is likely to be highly variable among individuals because of genetic differences. The specific genes involved have not been fully identified, so it is not possible to assess the variability when studying exposure-risk relationships epidemiologically. In these circumstances, the unmeasured variability in susceptibility contributes to error in the estimation of exposure-risk associations. It is also likely to be manifested as variability in the lag between exposure and sensitization or development of CBD. When studies are small and the disease outcome is relatively infrequent, we will expect to see considerable heterogeneity in the apparent strength of association between exposure and risk, even when exposure is well measured.

Ideally, studies of beryllium cohorts include BeLPT testing of all cohort members before the first exposure, but that is usually not possible. Often, employment for at least several months precedes the first test, and this may be sufficient time for sensitization to have occurred.

Another source of uncertainty is that we do not know the appropriate summary measure of exposure, or dose metric, and use of the wrong one can introduce bias, often (but not always) towards the null. The choice of summary measure depends on the disease mechanism. In the case of a cell-mediated immunity, one might expect short-term "peak" exposure to be more important than the same cumulative exposure delivered over a longer period. Exposure assessments rarely permit evaluation of the effect of very short peak exposure (hours or even minutes), but it is plausible to hypothesize that they are important in BeS. Madl et al. (2007) focused their attention on the year of highest exposure as a way to approach that, but the time scale was too long—the year of highest exposure might not determine the *minutes* of highest exposure. One might also expect exposure received after a person has become sensitized to contribute to risk differently from exposure before sensitization. Finally, some forms of beryllium are poorly cleared from the lungs and may contribute to risk long after exposure has ceased. As discussed in Chapter 4, the development of an animal model for CBD might provide insights into the temporal dynamics of the exposure-risk association and provide a rationale for preferring one dose metric to another.

Diversity of Physicochemical Form

The available literature covers a range of process steps from mining and milling (Deubner et al. 2001a) through refining and initial processing of beryllium metal (Kreiss et al. 1997; Rosenman et al. 2005), beryllioxide and beryllium-alloy production and machining (Kreiss et al. 1993a, 1996; Henneberger et al. 2001; Newman et al. 2001; Kelleher et al. 2001; Schuler et al. 2005; Stanton et al. 2006), nuclear-weapons manufacture (Kreiss et al. 1989, 1993b; Stange et al. 1996a,b, 2001), and weapons-facility cleanup (Viet et al. 2000; Sackett et al. 2004). It is of interest to understand whether there are differences in hazards between physicochemical forms of beryllium, and it may be possible to derive useful information by comparing risks among the different parts of the industry. In many cases, however, there are very few quantitative exposure data and many other differences in the studies that make it difficult to reduce them to "natural experiments" with different physicochemical forms of beryllium.

Limitations in the Study of Small Exposed Populations

Although the estimates of the current numbers of workers exposed to beryllium are in the tens of thousands, workers in facilities with regularly quantifiable exposure are far fewer. Many of the available studies are quite small, with typically only a handful of cases. And, because both BeS and CBD are prevalent outcomes knowledge of which depends on invasive medical monitoring, it is difficult to combine studies to increase statistical power. A study may have an initial population of several hundred workers, but—after accounting for incomplete participation in BeLPT screening, lack of bronchoscopy on all subjects, and the need for repeated sampling to confirm suggestive findings—there is often considerable uncertainty about the prevalence of CBD. Those and other important sources of uncertainty are not quantified with conventional measures of statistical significance or confidence intervals, so considerable caution should be exercised in assessing how much weight to give to a study's findings.

Healthy-Worker Effect

Occupational epidemiology is often handicapped by the healthy-worker effect, a tendency for employed populations to be healthier than the general population. One aspect of the problem, called the healthy-worker survivor effect, is the tendency for workers who become sick to leave the working population and thus to leave a selected group still in employment. Cross-sectional studies generally look at the people at work at a specific time, and could underestimate the amount of disease in the population because such studies do no include workers who may have left because of illness. Early studies of beryllium-exposed cohorts were probably affected by this problem inasmuch as it is known that some workers reacted acutely to the very high exposures in the 1940s through 1960s in the beryllium industry. How serious the healthy-worker–effect bias is in the more recent studies is less clear.

CLINICAL LITERATURE

There is a large body of clinical information on BeS and CBD. This section reviews the literature on diagnosis of and testing for BeS, describes the clinical presentation and diagnosis of and testing for CBD, discusses the natural history of CBD and its management, and describes the use of the BeLPT in surveillance of beryllium workers.

Diagnosis of and Testing for Beryllium Sensitization

As described above, beryllium exposure can cause chronic granulomatous disease in the lungs that is associated with the presence of lymphocytes that specifically respond to beryllium. Before the advent of the BeLPT, CBD typically was diagnosed when a worker presented with clinical symptoms and an abnormal chest radiograph or lung function. In the 1970s and 1980s, researchers learned that lymphocytes from blood or lungs of people with CBD proliferated in the presence of beryllium in vitro. That response was refined and developed into what we now know as the BeLPT. The use of the BeLPT allows the identification of BeS in the absence of CBD.

BeS itself is not a disease, but it is a valuable indicator in an occupational-health surveillance program because it identifies exposed workers who are at risk for CBD. As noted elsewhere in this report, the magnitude of the risk that BeS will progress to CBD is not known, and it probably depends on many factors, including the extent and timing of beryllium exposure, its physicochemical form, and genetic factors. The BeLPT is now used for screening of currently or formerly beryllium-exposed workers for BeS, for surveillance to identify patterns of exposure to beryllium in the workplace, and as part of the clinical evaluation in the differential diagnosis of some lung disorders.

The test involves an in vitro challenge of lymphocytes from either bronchoalveolar lavage (BAL) fluid or peripheral blood with beryllium salts. In beryllium-responsive people, the challenge induces an oligoclonal proliferation of sensitized lymphocytes that is measured on the basis of uptake of tritiated thymidine. Somewhat different protocols and criteria have been used, but BeLPT testing is becoming more standardized in the few laboratories in the United States that use it.

The test is performed by placing cells in primary culture in the presence and absence of beryllium sulfate, typically across a 3-log range of salt concentrations. Cell proliferation is measured according to the incorporation of tritiated thymidine into the dividing cells, typically at two points (4 and 6 days or 3 and 7 days) in culture. Results are expressed as a "stimulation index"—the ratio of radioactivity counts per minute in cells stimulated by beryllium salts to counts per minute in unstimulated cells. Each laboratory sets its own normal range for the test on the basis of data on healthy unexposed control subjects. A test typically is considered positive if two stimulation indexes are increased. The BeLPT, like other cell-culture assays, can be subject to intratest, intertest, and interlaboratory variability; therefore, before a person is considered sensitized, a positive, or abnormal, BeLPT result is generally confirmed by testing the same blood sample in a different laboratory or testing a later sample.

The BeLPT of peripheral blood or BAL cells is used in the diagnostic workup of patients who have interstitial lung disease and possible beryllium exposure when CBD is in the differential diagnosis. A positive BeLPT result differentiates CBD from other interstitial lung diseases (such as sarcoidosis and hypersensitivity pneumonitis). A great majority of patients with CBD have a positive BeLPT result when peripheral blood or BAL cells are used, whereas patients with sarcoidosis or other interstitial lung diseases do not. The BeLPT is very specific as a diagnostic test. When used in surveillance, although many workers with an abnormal BeLPT result do not have CBD, a confirmed abnormal blood BeLPT result is considered a strong predictor of CBD in workers with known exposure to beryllium. In cross-sectional studies (see Table 3-1), a variable but substantial percentage of workers (often over 50%) who are sensitized are found to have CBD after further diagnostic evaluation (Kreiss et al. 2007). In a longitudinal study of sensitized workers, the conversion rate from BeS to CBD in one cohort of workers followed for a mean of 4.8 years was 6-8% per year (Newman et al. 2005). More followup time is needed to determine the final lifetime risk in this group.

Interlaboratory variation in the blood BeLPT test has been described (Deubner et al. 2001b). Stange at al. (2004) presented data on a comparison of four laboratories in the United States that perform the BeLPT. Over 7,300 split samples were sent to the four laboratories, and each sample was tested at two. When one laboratory recorded an abnormal BeLPT result, the likelihood that a second laboratory would find the sample abnormal was 26.2%, 39.7%, and 32.4% in the laboratories that tested more than 200 samples. (The fourth laboratory, which tested only 123 samples, had higher agreement, 61.8%, but it was based on a relatively small number of samples.) When the comparison was restricted to people known to be sensitized (those who had two abnormal BeLPT results), a repeat sample in another laboratory had a likelihood of 80.4-91.9% of being found abnormal. In part because of potential interlaboratory variation, surveillance programs typically require two separate positive BeLPT results to determine BeS—a requirement that decreases the sensitivity of the test but increases the specificity. Donovan et al. (2007) reported on the performance of the BeLPT in a medical surveillance program. Workers with confirmed BeLPT tests often tested normal in a different laboratory--more evidence of interlaboratory variation. Cher et al. (2006), in an analysis of over 8,000 BeLPT tests, concluded that the variation between laboratories was systematic rather than random.

At the Third International Conference on Beryllium Disease in October 2007, Brousseau et al. reported on a study of concordance between two laboratories in Quebec when BeLPT testing procedures were closely matched. Some 500 split samples were sent simultaneously to both laboratories and analyzed as described in Table 3-2; 213 samples were abnormal or borderline in at least one laboratory. The concordance in results was close to 88% when a stimulation index (SI) was used as a measure and about 64% when the least absolute value (LAV) was used as a measure. The agreement improved to 98.1% with

TABLE 3-2 Testing Characteristics in Two Laboratories Performing the BeLPT

Characteristic	Laboratory A	Laboratory B
Volume of blood	30 mL	30 mL
Anticoagulant	Sodium heparin	Sodium heparin
Transit time	24 h	24 h
Gradient	Ficoll-Pack	Lympholyte H
Medium preparation	Phosphate-buffered saline	Phosphate-buffered saline
Culture medium	RPMI-1640	RPMI-1640
Mitogen	Phytohemagglutinin (10 μg/mL)	Phytohemagglutinin (10 μg/mL)
Incubation	4 d	4 d
Antigen	*Candida albicans* (20 μg/mL)	*Candida albicans* (20 μg/mL)
Incubation	6 d	6 d
Beryllium sulfate	10^{-4}, 10^{-5}, 10^{-6} M	10^{-4}, 10^{-5}, 10^{-6} M
Serum	10% AB	10% AB
Beryllium replicate	4	4
Mitogen replicate	4	4
Antigen replicate	4	4
Medium replicate	12	12
No. cells	2.5×10^5 cells/well	2.5×10^5 cells/well
^{3}H-thymidine	1 μCi/20 μL	1 μCi/20 μL
^{3}H-thymidine pulse	18 h	18 h
Scintillation cocktail	Betaplate Scint	Microscint 20
Report	Stimulation index	Stimulation index
Cutoff value	*f* (serum)	*f* (serum)
% coefficient of variation	35	35
Software	Microsoft Excel	Microsoft Excel

Source: Brousseau et al. 2007. Reprinted with permission from authors; copyright 2007.

the SI and to 88.5% with the LAV if a relatively discordant result was considered an agreement (one normal and one borderline result or one borderline and one abnormal result would be considered relatively discordant results). Only 1.9% of the comparisons with the SI and 11.5% with the LAV were truly discordant—one normal and one abnormal result.

New approaches based on flow cytometric analysis of $CD4^+$ T cells that respond to beryllium (Farris et al. 2000; Milovanova et al. 2004; Milovanova 2007) and the detection of beryllium-specific cytokine-secreting T cells with enzyme-linked immunosorbent spot assay (Pott et al. 2005) are under development.

Presentation and Diagnosis of and Testing for Chronic Beryllium Disease

The clinical definition and presentation of CBD have evolved with the development of the BeLPT. Formerly, when exposure was higher, workers typically could present with such symptoms as dyspnea, cough, fatigue, anorexia, weight loss, chest pain, and arthralgia. Physical examination findings reported by Stoeckle et al. (1969) included clubbing, skin lesions, peripheral lymphadenopathy, and splenomegaly. Renal calculi were also reported. Surveillance of beryllium-exposed workers with the BeLPT, starting in the 1980s, has enabled the diagnosis of CBD at an earlier stage when physical examination, chest radiography, and lung-function tests may yield normal results or show only minor abnormalities and the worker may have minimal or no symptoms. Surveillance-identified CBD can

progress to symptomatic lung disease and occasionally to advanced lung disease. Systemic manifestations of CBD can occur with more advanced disease and include fatigue, weakness, weight loss, and loss of appetite (Stoeckle et al. 1969).

Criteria for diagnosing CBD include the following (Newman et al. 1989; Pappas and Newman 1993; Maier et al. 1999):

- Evidence of beryllium exposure.
- Evidence of an immune response to beryllium, that is, positive responses in blood or BAL BeLPT tests. Those responses can also be considered evidence of exposure if exposure history cannot be ascertained.
- Histopathologic evidence consistent with CBD (see below).

A clinical evaluation for CBD generally includes a careful occupational history to assess exposure to beryllium, medical history, BeLPT testing, and medical evaluation with a focus on the lung. This evaluation generally includes spirometry, measurement of lung volume and diffusion capacity, chest radiography, and, if clinically indicated, high-resolution computed tomography (HRCT) of the chest. For a person with evidence of BeS and abnormalities that suggest the presence of interstitial lung disease, many clinicians would recommend bronchoscopy with BAL and transbronchial biopsy.

In the setting of surveillance-detected BeS in a worker with no other evidence of pulmonary disease, caution should be taken in evaluating the histopathologic findings in lung biopsies to avoid misclassifying workers as having CBD. Common histopathologic findings in CBD include nonnecrotizing granulomas and mononuclear-cell infiltrates.

Presentation of CBD ranges from the presence of histologic changes in lung biopsies consistent with CBD, but without symptoms, radiographic abnormalities, or decrements in pulmonary-function tests to end-stage lung disease with severe dyspnea, pulmonary-function decrements, radiographic abnormalities, hypoxemia, and cor pulmonale. Between the extremes, there may be mild to severe changes in one or more of the tests. The symptoms, radiographic changes, and pulmonary-function test findings are nonspecific for CBD, so other explanations need to be considered. (Normal pulmonary-function test results in a person who has CBD can reflect substantial declines for that patient, which may be apparent only if serial pulmonary-function test results are available with a true baseline for the person.) HRCT can detect abnormalities consistent with CBD when a chest radiograph or lung function appears normal. Thus, it can be difficult to determine whether mild disease is truly "subclinical" or constitutes a clinically significant effect; the term *subclinical CBD* has been used (Kriebel et al. 1988; Newman 1996) but not clearly defined. Other terms have also been used, such as *early CBD* (Rossman 1996) and *surveillance CBD* (Pappas and Newman 1993). For this report, *CBD* is used to refer to the full spectrum of CBD, as is done with other diseases (such as sarcoidosis and silicosis) that may be present despite the absence of detectable functional abnormalities or symptoms. The committee decided not to use the term *subclinical CBD* but to refer to CBD identified through screening as *surveillance-identified CBD*.

Histopathology

The largest study of the histopathology of CBD examined 124 cases of CBD from the Beryllium Case Registry (Freiman and Hardy 1970), which included workers in various industries (such as extraction and smelting, alloy production and processing, nuclear-weapons production, fluorescent-lamp manufacturing, and ceramic production). Patterns of diffuse noncaseating granulomas and various degrees of mononuclear-cell interstitial infiltrates were described in the lung-biopsy specimens obtained from open lung biopsies or autopsy material from those workers. Moderate to marked interstitial cellular infiltration was present in 80% (99 of 124) of the cases, and granulomas were absent or poorly formed in 44% (55 of 124). Some 20% (25 of 124) of the CBD cases had slight or absent cellular infiltration and

well-formed granulomas, and this group appeared to have a better prognosis than those with more cellular infiltration. No relationships were identified between the histologic pattern and the character of the industrial exposure or the timing of the illness. Giant cells, asteroid bodies in giant cells, and calcific inclusions were also noted. About half the cases had accompanying moderate to advanced interstitial fibrosis.

More recent studies have confirmed the histopathologic pattern of noncaseating granulomas, mononuclear-cell (lymphocytic) interstitial infiltrates, and less commonly interstitial fibrosis in lung specimens from transbronchial biopsies of patients with CBD (Newman et al.1989). Granulomas may not be detected in transbronchial biopsies, and a lymphocytic infiltrate may be the primary finding. The pathologic findings are not specific for CBD and may occur in other lung diseases, including sarcoidosis and hypersensitivity pneumonitis. In addition to noncaseating granulomas in the lung, extrapulmonary granulomas have been described in skin, liver, lymph nodes, and muscle in patients with CBD (Stoeckle et al. 1969).

Bronchoscopy, Bronchoalveolar Lavage, and Biopsy

Bronchoscopy with BAL and transbronchial biopsy is generally recommended for diagnosing CBD but is not without risk. Risks posed by bronchoscopy (such as oversedation, bleeding, and pneumothorax) vary with the individual patient's circumstances and are considered on an individual basis, as discussed in Chapter 7. Transbronchial lung biopsies are performed to determine the presence of nonnecrotizing granulomas and mononuclear-cell interstitial infiltrates; fibrosis may also be seen. The granulomas are histologically indistinguishable from those due to other granulomatous disorders, such as sarcoidosis and a granulomatous response to infection (without caseation).

BAL fluid is usually obtained by washing the middle lobe or lingula, and the fluid is sent for analysis of total and differential cell counts (to identify the presence of lymphocytosis), for culturing (to exclude infection as a cause of granulomatous changes), and to a specialized laboratory for a BeLPT of the BAL cells (rapid processing of the fluid with a specialized technique is needed) (Rossman et al. 1988; Newman et al. 1989).

BAL in CBD typically shows lymphocytosis (Rossman et al. 1988; Newman et al. 1989); the percentage of BAL lymphocytes may correlate with physiologic and radiographic disease severity. In some subjects with BeS and biopsy-confirmed CBD, BAL has shown normal percentages of lymphocytes (Newman et al. 2005). Because of the association between cigarette-smoking and increases in alveolar macrophages, cigarette-smoking may obscure BAL lymphocytosis. In addition, nicotine has been shown to inhibit lymphocyte proliferation (Kalra et al. 2000).

Pulmonary-Function Testing

Results of pulmonary-function testing in patients with CBD are variable; they include restrictive, obstructive, mixed-pattern, or isolated impairment in lung diffusion capacity. Milder cases can have minimal or no physiologic abnormalities. Sensitive physiologic measures have been reported to be increased ratio of dead space to tidal volume (V_D/V_T) on exercise testing (Pappas and Newman 1993) and an increased alveolar-arterial oxygen (A-a) gradient on exercising (Daniloff et al. 1997); both reflect impaired gas exchange, but neither is specific for CBD. Increased A-a gradient on exercising has also shown good correlation with HRCT-scan indications of CBD (Daniloff et al. 1997). In more advanced cases, decreased DLCO, restriction, airflow obstruction, and arterial hypoxemia may be present alone or in combination.

An early report from Andrews et al. (1969) of 41 patients studied for an average of 23 years after initial beryllium exposure showed a restrictive defect (20%); reduced diffusing capacity, normal lung volumes and airflow rates but reduced DLCO (36%); and an obstructive defect, which could have

included mixed obstruction and restriction (39%); and normal pulmonary-function tests (5%). The authors reported that the obstructive pattern occurred in both smokers and nonsmokers and was associated with peribronchial granulomas.

In a report of 12 patients with new diagnoses of CBD, pulmonary-function abnormalities were mild (Newman et al. 1989). One patient had restriction, and two former smokers had mild obstruction. Of the 12 patients, 11 had diffusing capacity that was normal when corrected for lung volume. Gas exchange on maximal exercise was normal in six of the nine patients tested.

Another study of 21 patients with CBD (defined as beryllium exposure, consistent biopsy results, and abnormal BeLPT results) identified through screening at their plants showed that 14 had normal pulmonary-function test results and 10 had normal physiologic measures on maximal exercise (Pappas and Newman 1993). Four had airflow obstruction, two had mixed obstruction and restriction, and one had abnormal DLCO). The 11 with abnormal exercise physiologic results showed increased V_D/V_T on exercise, abnormal gas exchange, or both. A comparison group of 15 CBD patients referred because of symptoms or radiographic abnormalities showed similar results, although fewer of them had normal pulmonary-function test results and exercise physiologic results.

Chest Radiography

Radiographic findings in CBD were first described as diffuse densities and hilar adenopathy (Weber et al. 1965; Stoeckle et al. 1969; Hasan and Kazemi 1974). Contraction of lobes with hyperinflation of adjacent lobes, calcifications in parenchymal densities and hilar nodes, pneumothorax, cysts, bullae, and linear scars were also described in advanced cases.

More recent studies of CBD that used the International Labour Organization classification system have described mainly diffuse, symmetric small opacities that were rounded, irregular, and of mixed patterns (Aronchick et al. 1987; Newman et al. 1994). Hilar adenopathy (always associated with interstitial abnormalities) was observed in 35-40% of people who had abnormal chest radiographs. Less common plain-film findings included coalescence of small opacities, linear scars, emphysematous bullae, retraction, distortion of lung architecture, and pleural thickening. Of those with biopsy-proven noncaseating granulomas, 46% had normal chest radiographs (Newman et al. 1994). The radiographic features of CBD are nonspecific and occur in other lung diseases, including sarcoidosis.

HRCT of the chest is more sensitive than plain chest radiography in identifying abnormalities in patients with CBD. However, in 25% of patients with biopsy-proven noncaseating granulomas, HRCT scans have not shown signs consistent with CBD (Newman et al. 1994). The most common HRCT findings in CBD are nodules and septal thickening. Other findings include ground-glass attenuation, pleural irregularity, bronchial-wall thickening, and hilar and mediastinal adenopathy. Honeycombing has been reported in clinically severe cases (Newman et al. 1994). The HRCT appearances of CBD are nonspecific and occur in other lung diseases, including sarcoidosis. In a study by Daniloff et al. (1997), there was a significant correlation between HRCT changes and impaired gas exchange on exercise.

Additional and New Tests

Newer tests and approaches for improving the diagnosis of CBD and elucidating disease progression are being developed but are not in regular clinical use. For example, measuring neopterin concentrations in peripheral blood has been proposed as a diagnostic adjunct that may correlate with CBD severity or progression (Harris et al. 1997; Maier et al. 2003a). A beryllium-stimulated neopterin test has been reported to have a sensitivity of 80-90% and a specificity of 87-100% (Maier et al. 2003a). Beryllium-specific T-cell cytokines (interferon-gamma and interleukin-2) that are detected in vitro in peripheral blood proliferation assays (Pott et al. 2005) have been proposed to differentiate BeS from CBD (Tinkle et al. 1997).

Progression and Management of Chronic Beryllium Disease

As noted earlier, CBD has a clinical spectrum that can range from evidence of BeS and granulomas of the lung without clinically significant symptoms or deficits in lung function to end-stage lung disease. Little has been published on the progression of CBD from no apparent functional impairment to functionally significant lung disease. The risk factors and time course have not been clearly delineated. Possible risk factors for progression that have not been systematically assessed include magnitude and type of beryllium exposure (including particle size and solubility), exposure duration, concurrent exposure to other lung toxicants, smoking, race, sex, life stresses, combat, surgery, and genetic factors (Newman 1996). Newman (1996) emphasized the need for prospective studies of the natural history of BeS and surveillance-identified CBD. Because of the highly variable rate of progression and presentation of signs and symptoms, Rossman (1996) recommended an annual assessment of CBD patients, including a history, physical examination, chest radiography, pulmonary-function tests, and exercise-physiology tests. In a cohort of 55 patients with BeS followed for 1-11 years, 17 (31%) developed CBD in an average of 3.8 years (range, 1-9.5 years) (Newman et al. 2005). Eleven of the 17 who progressed to CBD had at least one followup evaluation after CBD was diagnosed to determine progression. Average followup from CBD diagnosis to the most recent evaluation was 4.7 years. One of the 11 received oral steroid therapy 2 years after CBD was diagnosed. Longer followup will be needed to determine outcome in those with surveillance-detected CBD on a long-term basis.

Clinical management of CBD is modeled on the management of sarcoidosis. Oral corticosteroid treatment is initiated in patients who have evidence of progressive disease, although *progressive disease* is not well defined. In advanced cases of CBD (with respiratory symptoms and deteriorating pulmonary function that are considered as probably due to CBD), standard clinical practice includes the use of corticosteroids. In cases of CBD without physiologic impairment, whose diagnosis is usually based on transbronchial biopsy, the general approach is periodic re-evaluation, typically every 1-2 years, to look for deterioration in symptoms, pulmonary-function test results, or in chest radiographs. The decision to institute treatment with corticosteroids or other anti-inflammatory agents is made case by case.

Older reports, which appeared when beryllium concentrations were higher, indicated that deterioration can be rapid after the development of clinical disease. Hardy and Tabershaw (1946) followed 17 cases in young workers (age at symptom onset, 20-38 years) and described progression to death in five patients within 1-2 years. Improvement was noted in several workers, but the others had continuing disease that progressed rapidly in many cases. In some cases, exacerbation and remission were described. In others, a stable condition that lasted for years was followed by deterioration. Deterioration was described as worsening dyspnea, worsening lung function, worsening radiographic abnormalities, and in some cases the signs and symptoms of pulmonary hypertension and cor pulmonale. One patient returned to normal (with regard to symptoms and radiographic findings) after treatment with adrenocorticotropin (Stoeckle et al. 1969).

A more recent report of siblings with CBD showed clinical features similar to those reported earlier with progressive worsening of disease over 6 years despite steroid treatment (Tarlo et al. 2001). Since the report was published, one sibling has died, and the other has become oxygen-dependent. A third co-worker also has end-stage lung disease and has been assessed for heart-lung transplantation (case presentation at International Beryllium Meeting in Montreal 2005), and a fourth worker identified in the last year also has clinical disease requiring steroid therapy despite a BeLPT surveillance program (S. Tarlo, University of Toronto, personal communication, April 23, 2007).

No studies have measured the effect of removal from exposure to beryllium on sensitization or CBD. Other occupational diseases that result from immunologic sensitization to an occupational agent include hypersensitivity pneumonitis and occupational asthma. In both, the outcome is worse with continued exposure after disease develops. However, it is difficult to extrapolate those results to beryllium disease because both of the other conditions typically result in symptoms and pulmonary-function changes within hours after exposure. In addition, CBD has different clinical characteristics from either of the other diseases. Older cases of CBD in people who had not been removed from exposure appear to

have more severe disease compared with those who developed CBD more recently. However, it is not known whether that is due to the higher exposure concentrations of beryllium in former years, higher total pulmonary load of beryllium, or longer exposure after sensitization or onset of disease. It is unlikely that large cohorts of workers who are found to be sensitized to beryllium or have CBD will continue to work with beryllium exposure, and a research study to randomize workers to continue or avoid exposure would likely be considered unethical because of the potential severity of CBD. Therefore, the current clinical practice of a strong recommendation to remove CBD patients from exposure (Beckett et al. 2002; Kreiss 2005; Mapel and Coultas 2005 [p. 182, Box 10.1]; Maier et al. 2006) is appropriate. Offering it to those with BeS would also be prudent.

There is an absence of published data on possible modification of risk of sensitization and disease by demographic variables or differences in baseline health status. CBD that is diagnosed before there is any loss of pulmonary function would not generally need treatment with corticosteroids; however, removal from exposure to prevent progression of disease is an important rationale for early detection of CBD. The committee recognizes that, as with many such occupational restrictions, implementation can be difficult because of economic or other job-related concerns for individual workers and their families.

The diagnosis of CBD or BeS may be associated with psychosocial stress or loss of income. A case presentation at the 2005 International Beryllium Disease Conference in Montreal described a young man with surveillance-identified disease that resulted in job loss, major reactive depression, and unemployment (S. Tarlo, University of Toronto, personal communication, April 23, 2007). Although there are few published data on the psychosocial and economic consequences of a diagnosis of BeS or CBD, the committee recognizes the challenges of case management when there are potential psychosocial and economic implications. The committee believes that implementation of a comprehensive beryllium-exposure and -disease management program that includes appropriate worker education and counseling and medical-removal protection against lost wages (see Chapter 7) can minimize such potential adverse consequences. A more extensive examination of those issues lies outside the current scope of work.

Extrapulmonary Disease

Like sarcoidosis, CBD can have extrapulmonary manifestations; they are less common than in sarcoidosis, but few studies have systematically characterized them. As noted above, skin lesions used to be reported in workers exposed to beryllium salts (Kreiss et al. 2007) but much less commonly in workers exposed to beryllium-metal particles and dusts. Reported cutaneous manifestations of beryllium exposure include dermal granulomas and irritant and allergic contact dermatitis (Curtis 1951; Vilaplana et al. 1992; Berlin et al. 2003). The prevalence of those beryllium-related skin conditions appears to be relatively low, but epidemiologic studies have focused primarily on BeS and CBD.

Medical Surveillance of Beryllium-Exposed Workers with the Beryllium Lymphocyte Proliferation Test

Any test that is used in medical surveillance should have acceptable sensitivity, specificity, and predictive value. A diagnosis of BeS is usually followed by additional diagnostic testing for CBD with attendant risk and expense, so such a diagnosis must have an acceptable positive predictive value (PPV). Not all abnormal BeLPT results are confirmed by a second test on the same person or even on the same blood sample. Stange et al. (2004) reported on variation between laboratories when blood samples were split and sent to two laboratories simultaneously. The range of agreement on abnormal results was 26.2-61.8%, depending on the laboratories being compared; even between the laboratories with the highest agreement, 38.2% of abnormal BeLPT results were not confirmed by a second laboratory. Most guidelines for diagnosis of BeS require a confirmation of an abnormal BeLPT result with a second abnormal result; this reduces sensitivity while raising specificity. It is theoretically possible that someone

could have a confirmed abnormal BeLPT result but not be sensitized to beryllium, but there is no other test to measure sensitization to beryllium, so it is not possible to identify such cases confidently. The available evidence suggests that false positives are rare. For example, of 458 employees at Rocky Flats who were either new hires or employees with no known exposure to beryllium, none had a confirmed abnormal result (Stange et al. 2004). Silveira et al. (2003) combined data on three sites and found no confirmed abnormal results in over 1,000 people with no identified exposure. Donovan et al. (2007) reported that six (1.1%) of the new hires had confirmed abnormal BeLPT results, but all six had 18-50 days of exposure to beryllium between the initial positive test and a confirmatory BeLPT, and this leaves open the possibility that sensitization occurred after exposure began; the same study reported that a peak in the prevalence of confirmed abnormal BeLPT results occurred 4-8 months after the beginning of employment.

Because CBD has occurred in nonoccupational groups of people who lived near factories and cases can occur at very low levels of exposure, an apparent false positive may occur in a person who has nonoccupational exposure.

The essential question is how well the BeLPT predicts CBD; the answer can only be approximated. The usefulness of a screening test can be described according to its sensitivity, its specificity, its PPV, and its negative predictive value. Sensitivity is a measure of how well the test detects true positives, and specificity is a measure of how well it detects true negatives. The PPV is a measure of how many of those who test positive have the underlying condition; it is the ratio of true positives to all positives. A test with very good sensitivity and specificity may not have a good PPV if the disease prevalence is low in the population being screened. For example, if we use a test whose sensitivity is 99.9% and whose specificity is 99.9% in a population of 1,000,000 of whom 1% have the disease, we will detect 9,990 cases and miss 10 cases. However, we will also have 990 false positives and a PPV of 91%. As the specificity of the test declines or the underlying prevalence of disease declines, so does the PPV. Middleton et al. (2008) used the data from Stange et al. (2004) to estimate the PPV of a single or confirmed abnormal BeLPT result. They calculated that a confirmed abnormal result would have a PPV of 0.968 in a population with a 1% prevalence of BeS, and a single abnormal result would have a PPV of 0.383 in the same population. Middleton et al. estimate a PPV of 0.872 for a single abnormal result when the prevalence of BeS is 10%, but in most settings a single unconfirmed abnormal result has little value because of a low PPV for BeS.

Borak et al. (2006) argues that the PPV of the BeLPT is not high enough to meet current criteria for a good screening test. Their analysis of the PPV of the BeLPT for BeS is based on the use of a single test; current practice is to confirm a single abnormal test, and as Middleton et al. (2008) state, the PPV of the BeLPT can improve from 0.383 to 0.968 when a single abnormal BeLPT result is confirmed with a second abnormal result.

There are fewer data on which estimate the PPV of a confirmed abnormal BeLPT result for CBD. In one study that specifically addressed a beryllium-exposed population, Deubner et al. (2001b) calculated the PPV of the blood BeLPT in the Brush-Wellman workforce and reported that a single unconfirmed result had a PPV of 39% for CBD, a confirmed abnormal result had a PPV of 45% for CBD, and a split sample reported as abnormal in two laboratories had a PPV of 40% for CBD. Those values would decline as the prevalence of CBD declined. The ratio of people with CBD to all sensitized people (with and without CBD) is the PPV of the BeLPT. The PPV was 35% in the Rocky Flats workers described by Stange et al. (2004); about one-third of those who were sensitized also had CBD. The PPV varied between subgroups of the Rocky Flats workers; it was 14% in workers with fewer than 5 years of employment at Rocky Flats and increased to 65% in workers with more than 20 years of work at the facility.

The BeLPT is integral to any screening program. No alternative tests have been adequately validated to be put into practice outside research settings. The U.S. Air Force asked the committee to comment on five questions about the BeLPT. Each question is addressed below.

1. What is the value of a borderline or a true-positive BeLPT result in predicting CBD? A borderline BeLPT result in combination with a positive result is generally indicative of sensitization. If a borderline result is not preceded or followed by a positive result, the subject is not considered sensitized. An algorithm for interpreting BeLPT results is presented in Appendix B, and the role of a borderline result is defined in the algorithm. The committee considers a true-positive (or confirmed abnormal) blood BeLPT result to be a predictor of CBD in workers with known exposure to beryllium, but there are insufficient data to predict the risk of progression accurately.

2. What is the utility of the BeLPT in worker surveillance? The BeLPT identifies BeS in exposed workers. When used to identify at-risk populations, rather than as a screening or diagnostic test, the BeLPT has been shown to be valuable for identifying facilities or jobs that pose risk. Medical surveillance with the BeLPT has been able to detect BeS risk better than traditional air sampling because BeS can occur at low air concentrations of beryllium. The committee stresses, however, that BeLPT screening should not be used as the first line of defense against exposure.

3. What followup tests should be performed for workers with positive BeLPT results? Workers with positive BeLPT results should undergo further medical evaluation, which should generally include a medical and occupational questionnaire, pulmonary-function tests that include lung volumes and carbon monoxide diffusing capacity, and high-resolution computed tomography of the chest when indicated. After review of the test results, consideration should be given to performing bronchoscopy with bronchoalveolar lavage, transbronchial biopsy, and possibly other tests (see Chapter 7). In the clinical setting, the decision to perform those examinations is made case by case.

4. What is the likelihood of developing CBD after a true-positive test? Some studies have reported that CBD is diagnosed in up to 50% or more of screened workers who have positive BeLPT results, and the conversion rate from BeS to CBD has been estimated to be 6-8% per year (Newman et al. 2005). However, the conversion rate was based on only one cohort of workers. Although those with positive BeLPT results are at increased risk for CBD, the available evidence is insufficient to make quantitative predictions about the magnitude of the risk.

5. Is there a standardized method for achieving consistent test results in different laboratories? No standardized method is used in laboratories in the Unites States. As described above, Brousseau et al. showed that concordance in results between laboratories improved when testing procedures were closely matched (when such variables as dose, time, and controls were standardized). Concordance in laboratory testing and analysis and a standard testing algorithm should reduce variation between laboratories but will not address issues of the sensitivity and specificity of the test.

CONCLUSIONS

Epidemiologic studies have shown that BeS and CBD occur in settings where airborne exposure to beryllium is below the current standard of 2 $\mu g/m^3$ but do not indicate clearly how much lower such a standard would have to be to be protective. Studies have shown that the risk of CBD in workers depends on the industry and the process, but the available data are inadequate for estimating specific risks related to different forms of beryllium exposure. Thus, the committee concludes that it is not possible to estimate a chronic inhalation-exposure level that is likely to prevent BeS and CBD in settings where beryllium has the potential for being aerosolized. Existing medical-management programs designed to keep air, surface, and skin exposure as low as feasible have been successful in substantially reducing BeS and CBD in various beryllium industries.

RECOMMENDATIONS

In the absence of sufficient data to establish a chronic inhalation level for beryllium that is unlikely to result in BeS or CBD, the committee recommends that an exposure- and disease-management program be implemented by the U.S. Air Force to protect its workers. The program should involve industrial-hygiene assessments to identify potentially exposed workers, to eliminate as many job tasks involving exposure to beryllium particles as possible, and to minimize the number of workers performing those tasks; screening of potentially exposed workers for BeS; medical management of BeS and CBD; and stringent engineering and work-practice controls to keep beryllium exposure to the lowest feasible level. Important aspects of the exposure- and disease-management program are discussed in Chapter 7.

The Air Force should evaluate the feasibility of requiring concordance in testing procedures between laboratories performing its BeLPTs, and the committee recommends the use of an algorithm for interpreting BeLPT results (see Appendix B).

As noted several times in this chapter, there remain many important questions about BeS and CBD, including host and exposure risk factors and the natural history of BeS and CBD. Research to address these questions will be assisted by the Air Force developing a centralized surveillance database (see Chapter 7), which would include workplace and exposure data and clinical information obtained as part of the beryllium exposure- and disease-management program. In addition to facilitating evaluation of the effectiveness of the program over time, the database could be appropriately designed to be used as a resource by researchers.

4

Mechanisms, Genetic Factors, and Animal Models of Chronic Beryllium Disease

This chapter provides an overview of the pathogenesis of chronic beryllium disease (CBD) and the mechanism of action of beryllium in causing it. It also provides a summary of studies to identify the genetic components involved in susceptibility to CBD and of attempts to develop animal models to study the disease.

PATHOGENESIS AND MECHANISMS OF ACTION

As early as 1951, Sterner and Eisenbud proposed that CBD was an immune-mediated hypersensitivity reaction directed against the inhaled beryllium antigen. Even the earliest accounts of the disease described it as hypersensitivity of delayed onset, which fits with the present understanding of the cellular immune mechanisms underlying CBD. Although alterations in humoral immune characteristics have been described in CBD patients (Resnick et al. 1970; Cianciara et al. 1980), by and large the immunopathology of the disease involves cellular immune mechanisms. Moreover, beryllium is not defined by the Occupational Safety and Health Administration as a chemical sensitizer. That is, repeated exposure to beryllium does not cause an immediate immunoglobulin E–mediated allergic reaction. Beryllium-induced disease is believed to be contingent on cell-mediated (delayed-type hypersensitivity) immunopathology. Therefore, the term *beryllium sensitization* (BeS) refers to the $CD4^+$ T-cell immune response, which is measured with in vitro assays discussed elsewhere in this report.

Understanding of the immunologic basis of CBD and the immunopathogenic mechanisms that contribute to it has advanced, but many questions about the details of interactions between exposure and host factors remain. The literature of CBD is extensive, and this section consists of a selective review of the primary pertinent literature that has shaped current understanding of the immune mechanisms involved and of genetic factors that might contribute to susceptibility to the disease.

CBD is a systemic granulomatous disorder that affects the lungs predominantly. The mechanism underlying CBD pathogenesis involves an immune response to beryllium (Figure 4-1). $CD4^+$ T lymphocytes recognize beryllium as an antigen that triggers cell proliferation and release of cytokines and inflammatory mediators. The release of inflammatory mediators results in an accumulation of mononuclear-cell infiltrates and fibrosis that lead to the lesion typical of the disease—a noncaseating granuloma.

Critical Role of $CD4^+$ T Cells

Beryllium acts as a major histocompatability complex (MHC) class II restricted antigen that stimulates the proliferation and accumulation of beryllium-specific $CD4^+$ T cells in the lungs (Saltini et al. 1989, 1990). Two observations illustrate the primary importance of $CD4^+$ T cells in the pathogenesis of

CBD: the development of granulomatous inflammation in the lungs is associated with the accumulation of $CD4^+$ T cells in bronchoalveolar-lavage (BAL) fluid, and sensitization to beryllium is detected in the ability of $CD4^+$ T cells to proliferate in response to beryllium salts in culture.

The immunobiology believed to be associated with CBD provides a diagnostic test for BeS. As noted earlier, the beryllium lymphocyte proliferation test (BeLPT) involves an in vitro challenge of either BAL-derived or peripheral-blood–derived mononuclear cells with beryllium salts. In beryllium-responsive people, the challenge induces an oligoclonal proliferation of sensitized lymphocytes that is measured in a standard assay in which tritiated-thymidine incorporation occurs in proportion to DNA synthesis and blastogenesis (Rossman et al. 1988; Kreiss et al. 1989).

Because beryllium drives the proliferation and expansion of $CD4^+$ T cells in an antigen-restricted manner, T-cell lines and clones have been derived from the BAL fluid and blood of CBD patients. There are important differences between the antigen-specific T-cell clones found in the lungs of CBD patients and those in the circulation of beryllium-sensitized people, and the differences may have implications for the progression from BeS to CBD. For example, the T-cell receptor (TCR) repertoire in beryllium-reactive peripheral blood cells appears to be more diverse than that in the lungs of CBD patients (Fontenot et al. 1999). That suggests that a subset of T-cell clones expressing homologous TCRs has pathogenic potential. In many people, particularly CBD patients in the ceramics industry exposed to beryllium oxides, the T cells found in the BAL fluid express TCRBV3 genes with identical or homologous complementary-determining region 3 sequences. As further evidence that these are oligoclonal expansions, the beryllium-responsive T cells coexpress only a few homologous TCRα genes (Fontenot et al. 1999). That means that there is selective expansion or accumulation of some $CD4^+$ T-cell subsets in the lungs of CBD patients. The selectivity is probably related to the antigenicity of beryllium and probably provides clues to conventional antigen peptides that are modified by beryllium.

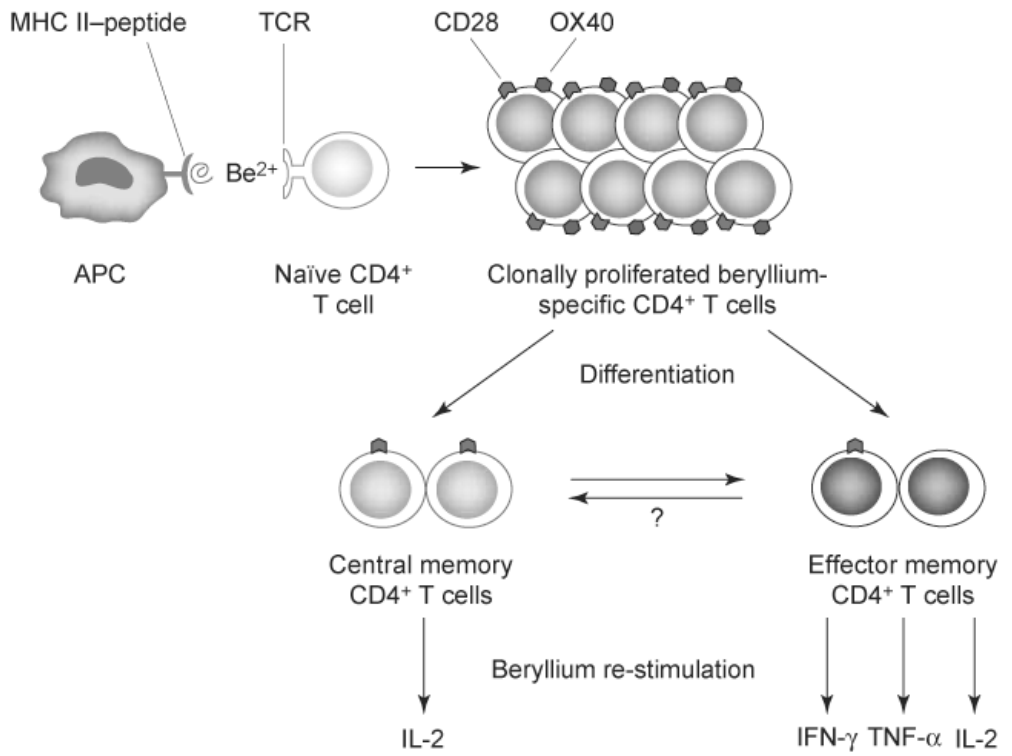

FIGURE 4-1 Immune response to beryllium. Source: Fontenot and Maier 2005. Reprinted with permission; copyright 2005, *Trends in Immunology*.

Antigen Processing and Presentation of Beryllium

As discussed above, sensitization to beryllium can be readily demonstrated in the ability of $CD4^+$ T cells to proliferate in response to beryllium salts in culture. The proliferative response has characteristics of a response to antigen, but the nature of the antigen recognized by $CD4^+$ T cells is not known. In studies of mouse lymphocytes, Newman and Campbell (1987) found that beryllium sulfate was mitogenic for B lymphocytes but not T lymphocytes. They did not address the potential for endotoxin contamination of the beryllium-salt preparation to drive the polyclonal B-cell response. On the basis of many human studies, it is reasonable to conclude that beryllium is not a mitogen for human lymphocytes. Proliferation of beryllium-specific $CD4^+$ T cells requires the engagement of clonotypic TCRs with an unknown beryllium antigen bound by MHC class II molecules on the surface of antigen-presenting cells.

The physicochemical properties of beryllium ions offer few clues to a better understanding of its immunogenicity. The immunogenicity of beryllium probably lies mainly in its ability to haptenate and thereby alter the structure of peptides that occupy the antigen-binding cleft of MHC class II molecules. Other metal ions—including nickel, cobalt, mercury, and gold—may elicit T-cell reactivity by similar mechanisms (Lawrence and McCabe 2002); however, the specific peptides and MHC molecules (pMHC) involved in all cases are different from those attributed to immune reactivity to beryllium. As with immune reactivities to other metal:pMHC, the response to beryllium:pMHC is exquisitely specific and lacks cross-reactivity with other metal:MHCs.

Knowing that susceptibility to CBD was associated with particular alleles of the class II human leukocyte antigen-DP (HLA-DP) molecule, Fontenot et al. (2000) examined whether the $CD4^+$ T-cell proliferation accompanying CBD involved the presentation of beryllium by HLA-DP. Beryllium-specific T-cell lines isolated from the lungs of CBD patients showed that the response to beryllium was almost completely and selectively blocked by monoclonal antibodies directed at HLA-DP. Additional studies with fibroblasts engineered to express only specific HLA-DP alleles demonstrated that the response to beryllium was restricted to haplotypes previously implicated in susceptibility to the disease. Hence, beryllium presentation by some HLA-DP alleles to $CD4^+$ T cells is the underlying mechanistic basis of CBD. Analysis of the amino acid residues shared by HLA-DP alleles that present beryllium revealed that those with a negatively charged glutamic acid residue at the 69th position of the β chain (Glu69) were especially capable of inducing a T-cell response (Richeldi et al. 1993; Wang et al. 1999; Fontenot et al. 2000; Lombardi et al. 2001; Bill et al. 2005). Not all CBD patients have a Glu69 containing HLA-DP allele. Indeed, t early work by Fontenot et al. (2000) demonstrated that anti-HLA-DR reagents partially inhibited T-cell responsiveness to beryllium in some cases. Recent work by Bill et al. (2005) reported an increased frequency of HLA-DR13 in some CBD patients who lacked a Glu69 HLA-DP allele. These HLA-DR13 alleles have a glutamic acid at position 71 of the β chain (which corresponds to position 69 of HLA-DP). Beryllium presentation to $CD4^+$ T cells might occur through an alternative HLA-DR Glu71 pathway that is capable of inducing beryllium-specific proliferation and interferon-gamma (IFN-γ) production by $CD4^+$ T cells. Genetic susceptibility to CBD is discussed later in this chapter.

Amicosante et al. (2001) conducted beryllium-binding assays with purified soluble HLA-DP molecules and beryllium sulfate and showed that the HLA-DPβGlu69 residue played a role in beryllium binding. Whether that involves a direct interaction between Glu69 and beryllium ions or beryllium modifies an unknown peptide that then preferentially interacts with the HLA-DPβGlu69 alleles is unknown (reviewed by Amicosante and Fontenot [2006]). Homozygosity, as opposed to heterozygosity, in the expression of the HLA-DPβGlu69 supratypic variant allele did not impart increased responsiveness, so the cell-surface density of class II molecules charged with beryllium-modified antigenic peptides does not dictate the intensity of responsiveness (Amicosante et al. 2005).

The nature of the beryllium antigen remains one of the key issues that require further study with respect to the immunopathogenesis of CBD. Amicosante et al. (2001) demonstrated that beryllium binds to HLA-DPβGlu69 at a pH of 5.0 and at a pH of 7.5. pH 5.0 mimics the acidic microenvironment where peptides are loaded onto HLA class II molecules, whereas pH 7.5 represents the extracellular environment where beryllium might bind to HLA-DP molecules directly at the cell surface. That beryllium binds to

HLA-DPβGlu69 at a pH of 7.5 suggests that it binds to HLA-DP in the absence of antigen processing. Furthermore, Fontenot et al. (2006a) demonstrated that paraformaldehyde-fixed beryllium-pulsed antigen-presenting cells stimulated the proliferation of $CD4^+$ T-cell lines derived from the lungs of CBD patients. That suggests that the presentation of soluble beryllium does not require antigen processing. Although direct antigen presentation of beryllium from soluble beryllium salts may occur, Stefaniak et al. (2005) reported that dissolution of beryllium oxide particles in macrophage phagolysosomes may be an important source of dissolved beryllium for input into the cell-mediated immune reaction characteristic of beryllium disease. The physicochemical state of beryllium (single-constituent vs multiconstituent material) influences its bioavailability, which may be tied to the initiation or sustainment of immune reactivity. Stefaniak et al. (2006) found that the dissolution rate stimulated by phagolysosomal fluid was greater for beryllium-copper–alloy fume than for beryllium oxide; this suggests that the physicochemical form of beryllium encountered in the workplace may have a bearing on initiating the sensitization process. Beryllium complexed with ferritin may be an important source of beryllium taken up by macrophages (Sawyer et al. 2004a). The uptake of beryllium may lead to aberrant apoptotic processes and the release of beryllium ions, which will continue the stimulation of T-cell activation (Sawyer et al. 2000; Kittle et al. 2002; Sawyer et al. 2004a). Beryllium uptake may be accompanied by oxidative stress and generation of reactive oxygen species that lead to the apoptotic response (Sawyer et al. 2005). It has been hypothesized that the interaction between the innate and acquired immune systems leads to the cyclical rerelease of beryllium into the lungs, where it elicits proinflammatory cytokine production and T-cell proliferation (Sawyer et al. 2002).

The beryllium-antigen–presenting cells themselves have not been well defined (L.A. Maier, National Jewish Medical and Research Center, personal communication, April 5, 2007). They may be macrophages, dendritic cells, or other professional antigen-presenting cells. Recently, self-presentation of beryllium by HLA-DP–expressing BAL $CD4^+$ T cells has been reported (Fontenot et al. 2006b). Self-presentation by BAL T cells in the granuloma results in activation-induced cell death, which may lead to the oligoclonality of the T-cell populations characteristic of CBD.

Th1 Cytokine Secretion by Beryllium-Specific T Cells

The $CD4^+$ T cells that accumulate in the lungs of CBD patients exhibit a Th1 phenotype and secrete such cytokines as interleukin-2 (IL-2), IFN-γ, and tumor-necrsis factor-alpha (TNF-α) (Tinkle and Newman 1997; Tinkle et al. 1997; Fontenot et al. 2002). Bost et al. (1994) were the first to show that alveolar macrophages from CBD patients produced increased concentrations of mRNAs for TNF-α and IL-6 but not for IL-1β, and the increase in mRNA was accompanied by an increase in TNF-α in BAL fluid. Tinkle et al. (1996) extended those observations and showed that the cytokines were released in response to beryllium stimulation and contributed to the unchecked inflammatory responses of effector macrophages and lymphocytes that are characteristic of the disease. The frequency of beryllium-specific Th1-cytokine–secreting $CD4^+$ T cells in the blood of beryllium-exposed people may prove to be a useful biomarker in discriminating between BeS and progression to CBD (Pott et al. 2005). The release of chemokines, including macrophage inflammatory protein-1 alpha and growth-related oncogene-1, may also lead to the migration of lymphocytes to the lung and the formation of the microenvironment that contributes to the development of CBD (Hong-Geller et al. 2006). The polarized Th1-like response to beryllium results in macrophage activation, accumulation, and aggregation and in the perpetuation of granulomatous inflammation seen in CBD.

Immunopathogenic Hallmarks of Chronic Beryllium Disease

The immunologic mechanisms underlying the progression of BeS to CBD are not well understood. Beryllium-sensitized people demonstrate a beryllium-specific immune response and show no

evidence of lung disease. In contrast, CBD is characterized by granulomatous inflammation and the accumulation of beryllium-responsive $CD4^+$ T cells in the lungs.

As mentioned above, the development of granulomatous inflammation in the lungs is associated with the accumulation of $CD4^+$ T cells in BAL fluid. Saltini et al. (1989, 1990) showed that increased frequency of mononuclear cells (macrophages and lymphocytes) in BAL fluid was a characteristic of CBD. Most of the BAL lymphocytes were $CD4^+$ T cells, the majority of which express markers consistent with an effector-memory T-cell (T_{EM}-cell) phenotype (such as $CD45RO^{hi}$, $CD62L^{lo}$, and $CCR7^{lo}$). These T_{EM} cells recognize the beryllium antigen in a CD28-costimulation–independent fashion, unlike beryllium-reactive cells in the periphery that require CD28 costimulation (Fontenot et al. 2003). A recent report by Palmer et al. (2007) extends that analysis of phenotypic characterization of $CD4^+$ subsets implicated in CBD by showing that expression of the CD57 marker is associated with inflammation and functional competence of the T cells in the lungs.

Progression from BeS to CBD is characterized by an increase in the frequency of beryllium-specific, Th1-cytokine–secreting $CD4^+$ T cells in the lung and granulomatous tissue. There appear to be important differences between beryllium-reactive memory $CD4^+$ T cells found in the lungs and in the peripheral blood of CBD patients (Fontenot et al. 2003). The differences include maturational differences in the memory T-cell compartment, as indicated by CD28-costimulation dependence of the $CD4^+$ beryllium-specific T cells in the periphery, and dissociation between Th1-cytokine secretion and lymphoproliferation in the periphery. Fontenot et al. (2005) compared the memory-cell phenotype of beryllium-reactive cells from CBD and BeS subjects and found that progression from sensitization to disease was associated with a differentiation of memory cells to an effector-cell phenotype (T_{EM}). Thus, an accounting of the frequency of T_{EM} cells in the blood of sensitized people may provide a means of monitoring disease progression. In other words, the beryllium-reactive $CD4^+$ T cells in the lungs of CBD patients are more differentiated than those in the blood of people who have BeS. Understanding the functional differences in $CD4^+$ T cells between the two compartments may be the key to understanding the immunopathogenesis of CBD and conversion from BeS and may lead to the development of biomarkers to identify people at greatest risk.

GENETIC SUSCEPTIBILITY

As noted in Chapter 3, not all people exposed to beryllium become sensitized, and not all who do become sensitized progress to develop CBD. Development of CBD appears to depend not only on the history of exposure to beryllium but on the genotype and phenotype of the person exposed. Attempts to identify the genetic components involved in susceptibility have centered primarily on the definition of CBD as a cell-mediated MHC class-II-restricted inflammatory disease. Accordingly, most studies have focused on specific genetic polymorphisms in MHC class II and proinflammatory genes, and a few others have considered the role of TCR-expression repertoires and other potential modifier genes.

Human Leukocyte Antigen Class II

In humans, the most gene-dense and polymorphic region of the genome is the MHC, which resides on chromosome 6p21.31. At the centromeric end of the MHC, spanning about 800 kilobases of DNA, sits the class II region (Acton 2001). It codes for HLA-DP, HLA-DQ, and HLA-DR—three heterodimeric proteins with limited tissue distribution (for example, to macrophages, monocytes, dendritic cells, and B lymphocytes) that are involved in antigen presentation and processing. The notion of a role of these genes in CBD arose from experiments that used lymphocytes derived from blood and BAL fluid of patients with the disease. Several studies demonstrated that antibodies directed against class II molecules blocked proliferation of lymphocytes in response to beryllium stimulation. The studies led to the idea that some HLA class II molecules may bind to beryllium and present it to T cells. Each class II

molecule consists of an α chain and a β chain, and the α_1 and β_1 domains of these chains form the peptide-binding domain of each molecule. Genes coding for those domains, which can be highly polymorphic, have been attractive candidates in genetic-association studies of CBD. Functional studies have also been used to study whether identified polymorphisms will result in differences in binding affinity and specificity for beryllium.

HLA-DP

In the HLA-DP heterodimer, the β chain displays far more polymorphism than the α chain. Some 23 alleles of HLA-DPα1 and 126 alleles of HLA-DPβ1 have been described as of April 2007 (EBI 2007). In a seminal study, Richeldi et al. (1993) first demonstrated the role of variants in the HLA-DPβ1 domain in CBD. That remains the best-studied and strongest genetic association in this disease. They identified 33 CBD patients defined by a history of occupational exposure, x-ray abnormalities, abnormal lung function, presence of granulomas, and a positive BeLPT result. The patients had a higher frequency of the HLA-DPB*0201 allele than 44 similarly exposed workers who had no manifestations of CBD (52% vs 18%) and a lower frequency of the DPB*0401 allele (27% vs 68%). The two alleles differ at position 69, where HLA-DPB*0201 has the amino acid glutamic acid instead of lysine. Further analysis showed that when all the alleles were considered, this Glu69 single-nucleotide polymorphism (GAG instead of AAG) was expressed in 97% of the CBD patients examined and 30% of the controls. HLA-DPB1 Glu69 appeared to be a definitive marker of susceptibility to beryllium disease.

Later studies, many by the same group, have reaffirmed the predominant role of the Glu69 variant in CBD but have suggested that its frequency is lower than originally thought (see Table 4-1). For example, Saltini et al. (2001) found HLA-DPB1 Glu69 to be present in only 73% of 22 cases studied. Given the relatively small samples involved in the studies, such a discrepancy is to be expected.

HLA-DP1 Glu69 and Sensitization

The original Richeldi et al. (1993) study left open the question of whether HLA-DP1 Glu69 was a marker of an immune response to beryllium—specifically, recognition and presentation—or simply a marker of disease susceptibility. Several studies have now evaluated HLA-DP1 Glu69 in BeS rather than in CBD itself. Wang et al. (2001) found the Glu69 substitution in 22 (88%) of 25 BeS people but in only 61 (37%) of 163 nonsensitized people. One study reported a much lower frequency of Glu69 in BeS subjects than in CBD subjects (Saltini et al. 2001), but other, larger studies have confirmed the initial finding and have shown Glu69 frequency to be similar in people with BeS and those with CBD (Rossman et al. 2002; Maier et al. 2003b; McCanlies et al. 2004).

HLA-DPB1 Glu69 is present in up to 48% of beryllium-exposed people who do not have CBD (McCanlies et al. 2003). Given the low frequency of the disease, that implies that most people with the Glu69 substitution do not develop the disease. Their failure to get CBD may be due in part to undocumented differences in workplace exposure to beryllium, coexposure to other environmental factors, or an inability to identify people in the early stages of the disease. Alternatively, other genetic considerations may be important. Using allele-specific DNA sequencing, Wang et al. (1999) showed that the specific allele carrying the Glu69 might be important. The most common HLA-DPB1 Glu69 allele is *0201; however, in a comparison of 20 people who had CBD and 75 controls, the strongest association with CBD was found with the rarer non-*0201 Glu69 alleles. Furthermore, the specific alleles for the α chain (HLA-DPA1) in the HLA-DPB1 Glu69 carriers were associated with disease development. The disparity in the importance of HLA-DPB1*0201 between this study and that of Richeldi et al. (1993) was attributed to the small number of probes and the less sensitive technique (partial regional-group–specific hybridization) used in the earlier study. Wang et al. (2001) studied the role of the alleles in BeS in a followup study of the same 20 CBD patients, 25 patients with positive BeLPT results but without CBD,

TABLE 4-1 Summary of Association Studies on HLA-DPB1 Glu69 and TNF-α as Susceptibility Factors in Chronic Beryllium Disease and Beryllium Sensitization

Reference	Subjects	Number Subjects	Frequency	Homozygosity	Alleles
HLA-DPB1 Glu69					Glu69
Richeldi et al. 1993	CBD	33	97%	—	0201: 52%
	Controls	44	30%	—	18%
Richeldi et al. 1997	CBD	6	83%	—	—
	Controls	121	30%	—	—
Wang et al. 1999	CBD	20	95%	30%	0201: 42% Non-0201: 80%
	Controls	34	45%	1.3%	68%
Saltini et al. 2001	CBD	22	73%	—	0201: 36% Non-0201: 41%
	BeS	23	39%	—	22% 17%
	Controls	93	40%	—	29% 11%
Wang et al. 2001	BeS	25	88%	24%	0201: 44% Non-0201: 52%
	Controls	163	38%	3%	25% 13%
Rossman et al. 2002	CBD	25	84%	Not associated with CBD	Non-0201: associated with CBD vs controls
	BeS	30	90%		
	Controls	82	47%	Data not shown	—
Maier et al. 2003b	CBD	104	86%	26%	0201: 39% Non-0201: 63%
	BeS	50	85%	15%	40% 56%
	Controls	125	38%	1.7%	24% 14%
McCanlies et al. 2004	CBD	90	82%	21%	—
	BeS	64	68%	16%	—
	Controls	727	33%	4%	—
TNF-α-308					Other Polymorphisms
Saltini et al. 2001	BeS, CBD	45	51%	—	—
	Controls	93	16%	—	—
Dotti et al. 2004	BeS, CBD	73	27%	—	TNF-α-1031, -863, -238; all not associated vs controls; TNF-α-857T increased in CBD
	Controls	43	5.8%	—	
Gaede et al. 2005	Europe, Israel CBD	13	15%	0%	—
	Controls	216	34%	4.6%	—
	United States CBD	39	44%	13%	—
	Controls	67	16%	1.5%	—
McCanlies et al. 2007	CBD	91	29%	2.2%	TNF-α-238: 8.9%
	BeS	63	38%	6.4%	13%
	Controls	722	28%	2.6%	12%
Sato et al. 2007	CBD	147	30%	0%	TNF-α-1031, -863, -857, -238; all not associated vs controls
	BeS	112	36%	2.5%	
	Controls	323	30%	2.3%	

ABBREVIATIONS: BeS, beryllium sensitization; CBD, chronic beryllium disease.

and 163 BeLPT-negative controls. The frequency of the rare non-*0201 Glu69 alleles was higher in BeS subjects (52%) than in controls (13%), and it appeared lower in BeS subjects than in CBD patients although this was not statistically significant. In particular, HLA-DPB1*1701 was overrepresented in CBD (30%) and BeS (16%) groups but rare in the controls (2%). Although those results are suggestive, there have been some concerns about misclassification of subjects. Studies by Rossman et al. (2002) and Maier et al. (2003b) have largely confirmed that the HLA-DPB1 non-*0201 Glu69 allele is more prevalent than HLA-DPB1*0201 in both CBD and BeS. One study found no differences between BeS

subjects and controls (Saltini et al. 2001), but it had a smaller study population and this smaller group was included in other genetic studies.

Using computational chemistry and molecular modeling, Weston et al. (2005) studied the HLA-DPB1 gene variants that were shown to code for Glu69. They assigned odds ratios for specific alleles on the basis of the studies cited above and found a strong correlation between the reported hierarchic order of risk of CBD and the predicted surface electrostatic potential and charge of the corresponding isotypes. They concluded that alleles associated with the most negatively charged proteins carry the greatest risk of BeS and CBD.

Another unresolved issue is whether copy number affects sensitization and disease. In the studies by Wang et al. (1999, 2001), HLA-DPB1 Glu69 homozygotes were seen only at very low frequencies in the control groups (1.3-3%) but at 24% and 30% in the BeS and CBD groups, respectively. Maier et al. (2003b) showed a similar frequency (26%) in CBD patients and concluded that Glu69 homozygosity conferred the greatest risk for CBD; however, they did not find that it was a risk factor for BeS. That led to the conclusion that Glu69 homozygosity may be important in disease progression. McCanlies et al. (2004), in a study of 884 beryllium workers (including 90 with CBD and 64 with BeS), also found increased HLA-DPB1 Glu69 homozygosity in those with CBD (21%) or BeS (16%). However, they argued, on the grounds that the HLA-DPB1 Glu69 genotypic distribution did not conform to Hardy-Weinberg population laws in CBD cases but did in BeS cases and controls, that it is the presence of those alleles rather than homozygosity itself that confers risk. The mechanism by which homozygosity would enhance an immune response is unclear. The issue is complicated by the finding that expression of HLA-DP Glu69 in the BeLPT determines higher T-cell proliferation rates but that homozygotes do not show greater proliferation than heterozygotes (Amicosante et al. 2005).

Gene-Environment Interaction

In a cross-sectional study of 127 workers, Richeldi et al. (1997) found that CBD was 8 times more likely in machinists (who have the greater exposure to beryllium) with HLA-DPB1 Glu69 than in those without this variant and was 7 times more prevalent than in nonmachinists with HLA-DPB1 Glu69. Those results suggest a potent additive gene-environment interaction, but the number of cases was very small (six), and this issue has yet to be addressed adequately in a larger setting.

HLA-DQ and HLA-DR

The original report that identified the importance of HLA-DPB1 Glu69 in CBD found no relationship between CBD and HLA-DR or HLA-DQ (Richeldi et al. 1993). However, because many CBD patients (3-27%) do not have Glu69, other MHC class II molecules have been investigated. The huge number of alleles involved, the small populations studied, and the relative lack of appropriate tools have limited the studies, and their results have been equivocal. The most consistent finding has been an increased frequency of HLA-DR13 alleles in those lacking HLA-DPB1 Glu69 (Rossman et al. 2002; Maier et al. 2003b; Amicosante et al. 2005). Support for this association comes from the finding that those with the alleles have a glutamic acid at position 71 of the β chain, which corresponds to Glu69 of HLA-DP. Functional experiments show that this Glu71 is essential for beryllium presentation by HLA-DR to $CD4^+$ T cells (Bill et al. 2005).

Associations between HLA-DQ markers and BeS or CBD in people lacking HLA-DPB1 Glu69 have been reported, but they have been attributed primarily to linkage disequilibrium with HLA-DR (Amicosante et al. 2005; Maier et al. 2003b).

Tumor-Necrosis Factor-α

The gene for TNF-α is telomeric to the class II loci. This proinflammatory cytokine is thought to play a key role in CBD. High TNF-α concentrations have been associated with more severe pulmonary disease in CBD. In addition, beryllium stimulation of $CD4^+$ T cells from the BAL fluid of CBD patients, but not BeS or sarcoidosis patients, will potentially induce TNF-α production (Sawyer et al. 2004b). The process appears to be transcription-dependent in that beryllium exposure specifically upregulates the AP-1 and NF-κB transcription factors (Sawyer et al. 2007). Accordingly, several studies have evaluated functional polymorphisms in the promoter of the TNF-α gene and their role in BeS and CBD.

The most commonly studied is the polymorphism with a G to A transition at the 308 position, which has been shown by many to be associated with increased TNF-α production and disease severity in a variety of conditions. In a small study, Maier et al. (2001) confirmed that this polymorphism was also associated with increased beryllium-stimulated BAL-cell TNF-α production by studying CBD patients who had been classified as high (20 cases) or low (10 cases) TNF-α producers. Saltini et al. (2001) saw associations between the TNF-308A polymorphism and both BeS and CBD in a population of 639 workers. In a followup study of the same cohort, Dotti et al. (2004) extended the results and reported that TNF-308A alleles were more prominent in the 73 subjects with either BeS or CBD (26.7%) than in the 43 controls (5.8%). Moreover, a similar association was observed for another polymorphism, TNF-857T. Jonth et al. (2007) studied polymorphisms in the transforming growth factor β1 (TGF-β1) gene and found no significant differences in TGF-β1 variants or haplotypes between CBD patients and controls. Within the CBD group, however, the TGF-β1 variants were found to be associated with a more pronounced decline in lung-function and gas-exchange measures. TGF-β polymorphisms have been associated with lower TGF-β production in other models, so those variants may be mechanistically linked to the immune dysregulation underlying CBD. Gaede et al. (2005) suggested that genetic background might also play a role in the importance of the TNF-308 allele. They reported that the high TNF-α–producing variant was present at increased frequency in CBD patients in the United States but not in those in Europe and Israel, but it is likely that the two groups had different beryllium exposure and disease severity.

Recent large-scale studies have cast doubt on earlier findings of the importance of TNF-α polymorphisms in CBD. McCanlies et al. (2007) found no relationship between CBD and either TNF-308 or TNF-238 in a large population-based study (886 beryllium workers, including 92 with CBD and 64 with BeS). Furthermore, contrary to previous reports by one group (Saltini et al. 2001; Amicosante et al. 2001; Rogliani et al. 2004), no interaction between HLA-DP1 Glu69 and either allele could be seen. Similarly, in probably the most thorough examination of the question to date, Sato et al. (2007) compared CBD patients (147), BeS subjects (112), and healthy beryllium-exposed controls (323) and studied five TNF-promoter single-nucleotide polymorphisms (including all those studied previously) and six relevant haplotypes. They reported that although some alleles and haplotypes might be associated with constitutive and beryllium-stimulated BAL-cell TNF-α production, they were not risk factors for either CBD or BeS. The discrepancies between past studies showing associations and the more recent studies may be due to misclassification, exposure differences, linkage disequilibrium between HLA-DRB1 and TNF-α genes, or statistical power.

Other Modifier Genes

Despite the assumption that CBD is a multigenetic disease, few genes outside the MHC loci have been carefully studied. Maier et al. (1999) studied polymorphisms in the gene for angiotensin-1–converting enzyme (ACE), a vasodilatory proinflammatory peptide, because of the observation that serum ACE activity is associated with CBD severity (Newman et al. 1992). They did not find any differences in ACE genotype between CBD patients and controls, nor did they find any statistically significant associations between ACE genotype and markers of disease severity or BeLPT results. Gaede et al. (2005) did find an association between polymorphisms in the transforming growth factor β1 (TGF-β1)

gene and CBD. However, TGF-β has not been measured in serum or BAL fluid of CBD patients, so the functional relevance of the association is unknown. Bekris et al. (2006) compared 29 healthy beryllium-exposed people, 27 BeS subjects, and 30 CBD subjects and observed associations between functional polymorphisms in the gene for glutamate cysteine ligase (GCLC TNR 7/7 and GCLM-588 C/C), an enzyme involved in glutathione synthesis, and CBD but not BeS. Because CBD is characterized by a Th1 cytokine response in the lungs and increased glutathione is thought to favor a Th1 response and is observed in the lungs of CBD patients, the results are functionally plausible; but they need to be confirmed in larger studies.

Recent gene-expression studies of beryllium-naive peripheral-blood mononuclear cells stimulated with beryllium have shown upregulated expression in many inflammation-related genes (Hong-Geller et al. 2006). Similar studies of CBD lung tissues will provide likely candidates.

ANIMAL MODELS OF PULMONARY IMMUNOTOXICITY AND SENSITIZATION

Beginning in the early 1950s, studies were conducted with beryllium to determine its chemical toxicity (see Table 4-2). Generally, the studies evaluated effects in several species given beryllium in various doses and chemical forms, via different exposure routes, and over different periods. Most studies provided evidence of beryllium-induced chemical toxicity in the lungs, such as lipid and enzyme changes indicative of lung damage and nonspecific inflammation (e.g., Hart et al. 1984; Sendelbach and Witschi 1987; Sendelbach et al. 1989; Finch et al. 1994). Foreign body granulomas have also been reported in some species, such as the rat (Robinson et al. 1968; Haley 1991). The studies have also generally shown that more soluble forms of beryllium are more toxic than insoluble forms (Hall et al. 1950; Schepers 1964; ATSDR 2002). Below we review the animal studies that have attempted to replicate the immunologic and pathologic features of human CBD.

As it became apparent that the immune system plays an important role in CBD, numerous attempts were made to develop animal models representative of human CBD (e.g., see review by Finch et al. 1996; Mroz et al. 2001). The studies were conducted with well-characterized laboratory-produced aerosols so that the importance of the chemical form and particle size of the beryllium aerosols could be evaluated. Haley et al. (1989) evaluated the effects of inhaled beryllium oxide calcined at 500°C or 1,000°C in beagles. The beryllium was inhaled only once, but there was prolonged retention in the lungs because of the relative insolubility of beryllium oxide. Peribronchiolar and perivascular changes in the lungs that progressed to granulomatous pneumonia were observed. The changes were more severe in dogs exposed to the 500°C beryllium oxide than in dogs exposed to the 1,000°C beryllium oxide. Higher calcination temperatures generally decrease the solubility and toxicity of beryllium and probably contributed to the difference in response. Peripheral blood lymphocytes responded to beryllium challenge in vitro, but positive proliferation results for lung lymphocytes were observed only in samples taken from dogs with high lung burdens of 500°C beryllium oxide. The granulomatous lung response was thought to be similar to that observed in humans with CBD, but the granulomas appeared to resolve within a year after the single treatment.

In a followup to that study, Haley et al. (1992) exposed the same dogs to the same forms of beryllium oxide (single inhalation exposure) 2.5 years after the first exposure and achieved lung burdens of 17 and 50 μg/kg. Lung histology showed perivascular and interstitial lymphocytic infiltrates with progression to patchy granulomatous changes and focal septal fibrosis. Beryllium-induced proliferation of blood and lung lymphocytes was also demonstrated. Beryllium cleared from the dogs according to a two-component negative exponential function. The first component had a half-life of 44 days, and the second a half-life greater than 1,000 days. The skeleton and the lungs each contained about half the beryllium in the body at the time of sacrifice (210 days after exposure). The authors concluded that "[beryllium]-induced granulomatous and fibrotic lung lesions are accompanied by [beryllium]-specific immune

TABLE 4-2 Selected Pulmonary and Immunologic Toxicity Studies in Animals

Reference	Species	Route	Dose	Findings
Single Exposure				
Robinson et al. 1968	Dog	Inhalation	Be at 115 mg/m^3 from BeO, BeF_2, $BeCl_2$ (single); particle size 30% > 5 µm; detection limit, 1 µm	Ultrastructure changes in lungs indicative of foreign-body reaction
Kang et al. 1977	Rabbit	Intradermal	10 mg $BeSO_4$ (single)	Sensitization, skin granulomas
Barna et al. 1981	Guinea pig	Endotracheal	10 mg BeO (single); mean particle size, 5 µm	Granulomas, interstitial infiltrate with fibrosis with thickening of alveolar septae
Barna et al. 1984	Guinea pig	Endotracheal	5 mg BeO (single)	Granulomatous lesions in strain 2 but not strain 13 guinea pigs
Hart et al. 1984	Rat	Inhalation	Be at 500 ± 4.1 ng from BeO (single, lung burden; particle size, 90% with mean diameter ≤ 1 µm	Lipids and enzymes increased in BAL fluid
Sendelbach and Witschi 1987	Rat	Inhalation	Be at 3.3 or 7.0 µg/L from $BeSO_4$ (single); particle size, 1.95 µm, GSD = 1.38, at 3.3 µg/L; 2.0 µm, GSD = 1.85, at 7.0 µg/L	Enzyme changes in BAL indicative of lung damage
	Mouse	Inhalation	Be at 7.2 µg/L from $BeSO_4$ (single); particle size, 1.85 µm, GSD = 1.59	
Votto et al. 1987	Rat	Intratracheal	2.4 mg $BeSO_4$ (after subcutaneous immunization with 8 mg/mL $BeSO_4$ at 2-wk intervals)	Granulomas, T-cell subsets in BAL and lung tissue not correlated
Haley et al. 1989	Dog	Inhalation	17 and 50 µg/kg BeO (single, lung burden)	Granulomas, evidence of immune response, low-fired beryllium more toxic
Sendelbach et al. 1989	Rat	Inhalation	Be at 4.05 µg/L from $BeSO_4$ (single); particle size, 1.9 µm, GSD = 1.89	Focal interstitial pneumonitis
Haley et al. 1990	Rat	Inhalation	800 µg/m^3 (single; initial lung burden, 625 µg)	Acute pneumonitis
Haley et al. 1992	Dog	Inhalation	17 and 50 µg/kg BeO (two doses, lung burden)	Granulomatous pneumonia with focal septal fibrosis
Huang et al. 1992	Mouse	Intratracheal	$BeSO_4$: immunization with 5 µg Be (3 doses), challenge with 1-5 µg Be $BeSO_4$: immunization with 5-50 µg Be (3 times biweekly), challenge with 1-5 µg Be BeO: 4, 20, and 100 µg	Granulomas produced in A/J strain but not BALB/c or C57BL/6
Finch et al. 1994	Rat	Inhalation	0.32, 1.8, 10, and 100 µg Be (single, lung burdens)	Acute pulmonary toxicity, progression of acute to chronic toxic responses

(Continued)

TABLE 4-2 Continued

Reference	Species	Route	Dose	Findings
Haley et al. 1994	Monkey	Intrabroncheal	1, 50, and 150 µg Be 2.5, 12.5, and 37.5 µg BeO; particle size, for BeO, 1.6 µm; GSD = 1.9; for Be, 1.4 µm; GSD = 1.4	Pulmonary toxicity differed between chemical form of beryllium (oxide less toxic than metal)
Nikula et al. 1997	Mouse	Inhalation	62 ± 18 µg Be (lung burden) for C3H/HeJ strain (normalization for body weight, 3.6 ± 0.5 µg/g Be); 49 ± 16 µg Be (lung burden) for A/J strain (normalization for body weight, 3.2 ± 1.3 µg/g; particle size, 1.4 µm, GSD = 1.9	Pneumonitis
Benson et al. 2000	Mouse	Intratracheal	12.5, 25,and 100 µg BeCu; 2 and 8 µg Be (single)	Acute lung toxicity associated with alloy exposure by not metal exposure
Tinkle et al. 2003	Mouse	Dermal	25 µL of 0.5 M $BeSO_4$ 70 µg BeO in petrolatum	Lung microgranulomas; some resolved
Repeated Exposure				
Hall et al. 1950	Cat, dog, guinea pig, rabbit, rat, monkey	Inhalation	10-88 mg/m^3 BeO powders (6 h/d, 5 d/wk, for 56-360 h total) $BeSO_4$•$4H_2O$ fired at 1,350°C (median particle size, 5 µm) $BeSO_4$•$4H_2O$ fired at 1,150°C (median particle size, 12.7 µm) BeO•$2H_2O$ fired at 1,150°C (median particle size, 0.45 µm) $Be_4O(C_2H_3O_2)_6$ at 400°C (median particle size, 0.38 µm)	Hematologic and pulmonary toxicity observed in all species. Rats had highest acute toxicity. $Be_4O(C_2H_3O_2)_6$ at 400°C was the most toxic, authors suggest likely due to small particle size and more extensive distribution.
Scheppers 1964	Monkey	Inhalation	27 µg/ft^3 BeF_2 (5.2 µg/ft^3 Be) 66 µg/ft^3 $BeSO_4$ (5.6 µg/ft^3 Be) 66 µg/ft^3 $BeHPO_4$ (5.6 µg/ft^3 Be) 66, 373 µg/ft^3 and 2.75 mg/ft^3 $BeHPO_4$	BeF_2 more toxic than $BeSO_4$ and $BeHPO_4$.
Marx and Burrell 1973	Guinea pig	Intraperitoneal, intradermal	2.6 mg $BeSO_4$ (1 injection/wk for 2 wk); 10 µg $BeSO_4$ (12 biweekly injections)	Sensitization
Kang et al. 1977	Rabbit	Intradermal	1.4 mg $BeSO_4$ (cumulative dose, administered 2 time/wk for 6 wk)	Sensitization
Eskenasy 1979	Rabbit	Intramuscular	10 mg/mL $BeSO_4$ (5 injections at 7-d intervals)	Sensitization, berylliosis
Goel et al. 1980	Rat	Oral	20 mg $Be(N0_3)_2$ (40 doses over 2.5 mos)	Pulmonary toxicity (histopathology and enzymology of the lungs)
Freundt and Ibrahim 1990	Rat	Oral	100 ppm $BeSO_4$ for 91 d (drinking water)	Increased body weight gain

responses within the lung" (p. 400). However, there was no correlation between the presence or severity of lesions and previous exposure or pulmonary immune response to beryllium oxide. Also, the lesions were not cumulative with sufficient latency time between the exposures.

Haley et al. (1994) conducted studies in cynomolgus monkeys given beryllium oxide (calcined at 500°C) or beryllium metal by bronchoscopic instillation. Lymphocytes were increased in the BAL fluid after 14, 30, or 90 days in monkeys treated with beryllium metal and after 60 days in monkeys treated with beryllium oxide. BAL lymphocytes from monkeys exposed to beryllium metal, but not monkeys exposed to beryllium oxide, responded positively in the BeLPT. The lungs of monkeys treated with beryllium metal showed inflammation, interstitial fibrosis, and type II cell hyperplasia; some also had discrete granulomas. Smaller and fewer lesions were found in monkeys treated with beryllium oxide. Whether the lesions resolved over time as in other animal models was not reported.

In a review of the work described above, Finch et al. (1996) concluded that although dogs and monkeys respond to beryllium by developing granulomatous lung lesions with a substantial lymphocytic component and their lymphocytes exhibited a beryllium-specific proliferative response in vitro, the lesions failed to progress. Thus, neither species was a good model of the progressive CBD seen in people.

Studies in guinea pigs exposed to beryllium oxide have also produced granulomatous lung disease and evidence of immune sensitization to beryllium. Barna et al. (1981, 1984) administered intratracheal injections of 5-10 mg of beryllium oxide to outbred Hartley guinea pigs and two inbred strains of guinea pigs (strains 2 and 13). Six weeks after exposure, the Hartley and strain 2 guinea pigs, but not strain 13, developed granulomatous lung changes typical of human CBD, with numerous granulomas, mononuclear interstitial infiltrates, and fibrosis. The Hartley and strain 2 guinea pigs also showed evidence of beryllium sensitization, with positive delayed-type hypersensitivity skin tests and in vitro proliferation of lymphocytes in response to beryllium sulfate. Intravenous or oral exposure to beryllium sulfate induced tolerance to the intratracheally administered beryllium oxide. The lung granulomas and beryllium sensitization were also mitigated by treatment with prednisone, L-asparaginase, or cytoxan. The authors concluded that the inbred strain differences in susceptibility to beryllium implicated genetically determined immune mechanisms similar to human CBD. The lung granulomas in strain 2 guinea pigs appeared to be resolving 1.5 years after exposure even though lung tissues still contained beryllium (Barna et al. 1984).

Different mice strains have also been used in attempts to develop an animal model that mimics human CBD. For example, Nikula et al. (1997) demonstrated chronic granulomatous pneumonia and lymphocytic responses induced in A/J and C3H/HeJ mice by a single inhalation of beryllium metal at 1,030 mg/m^3 for 90 min. Granulomas with increased numbers of CD4+ cells, epithelial hyperplasia, and inflammatory cells were detected in the lungs of both strains of mice at 28 weeks, but beryllium-specific lymphocytic proliferation could not be demonstrated. The authors suggested that this response in mice was associated with T-cell delayed hypersensitivity and not a foreign body reaction as observed in rats. Finch et al. (1998a) exposed C3H/HeJ mice to beryllium-metal aerosols in a single exposure to achieve lung burdens of 1.7-34 μg. Particle clearance was impaired at lung burdens of 12 and 34 μg through day 196. Increased numbers of inflammatory cells were detected in the BAL fluid of mice with the two highest lung burdens. Granulomatous changes were seen histologically beginning on day 8 in mice with lung burdens of 12 and 34 μg and on day 15 in mice with 2.6 μg. Beryllium sensitization and persistence of the granulomas were not observed..

Huang et al. (1992) investigated beryllium-induced pulmonary granuloma with different mice strains and different immunization and challenge protocols. Granulomas and beryllium sensitization were found only in A/J mice treated with beryllium sulfate, and the granulomas regressed within 20 weeks. Similar experiments with beryllium sulfate in BALB/c and C57BL/6 mice did not produce any lung granulomas, nor were granulomas induced in mice treated with a single intratracheal instillation of beryllium oxide. In general, A/J mice appear more prone to develop granulomas in response to beryllium than BALB/c, C57BL/6, or other mice strains.

Mice have also been sensitized to beryllium by intradermal and dermal exposures (Huang et al. 1992; Tinkle et al. 2003). Tinkle et al. (2003) sensitized C57L/6 mice to beryllium sulfate and beryllium

oxide by using skin exposure followed by a single intratracheal instillation or nose-only inhalation of beryllium. Ear swelling was used as an indicator of a delayed-type hypersensitivity reaction. Some mice developed lung microgranulomas, but they resolved spontaneously.

Unlike dogs, mice, and nonhuman primares, rats similarly exposed to beryllium do not appear to develop an immune granulomatous response. Haley et al. (1990) studied the toxicity of beryllium metal after a single nose-only exposure of F344 rats at 800 μg/m^3 for 50 min. Rats developed acute, necrotizing, hemorrhagic, exudative pneumonitis and intra-alveolar fibrosis that peaked on day 14. The authors concluded that human CBD is "an immunologically mediated granulomatous lung disease, whereas beryllium-induced lung lesions in rats appear to be due to direct chemical toxicity and foreign-body-type reactions" (p. 767).

Finch et al. (1994) studied the acute and chronic effects of beryllium metal administered nose-only to F344 rats to achieve lung burdens of 0.32-100 μg. Sacrifices were performed periodically for up to a year after exposure. The lowest lung burden of beryllium that induced pulmonary toxicity was 1.8 μg. At burdens of 10 and 100 μg, particle clearance from the lung was reduced, and pulmonary inflammation was observed, but typical immune-mediated lung granulomas were not observed. Lung lesions (fibrosis, chronic inflammation, and epithelial hyperplasia) were evident in the 100-μg group after 8 days of exposure. BAL fluid from rats with histologic alterations had nonspecific increases in neutrophils and proteins. Rats were affected at lung burdens below doses that affected mice.

Few studies have investigated beryllium-metal alloys. Benson et al. (2000) performed biodistribution studies in C3H/HeJ mice given particles of beryllium-metal or beryllium-copper alloy (2% beryllium and 98% copper) intratracheally. The alloy was given at 12.5, 25, or 100 μg, and beryllium metal was given at 2 or 8 μg. That acute lung toxicity and death were associated with the alloy but not with the metallic beryllium powder suggested copper toxicity. Pulmonary clearance of beryllium was found to be much slower than clearance of copper. Zissu et al. (1996) found that beryllium-copper alloys were more potent sensitizers of outbred guinea pigs than were soluble beryllium salts after intradermal injection.

CONCLUSIONS

Although animal studies in different species have demonstrated immunologic responses or pathologic changes similar to human CBD, animal models developed to date have varied between species, and none has adequately replicated the key features of human CBD, especially the persistence of granulomatous changes in the lung. The reason for the differences remains unclear, but the specific genes responsible for CBD in humans might not be present in animals. Thus, animal studies cannot reliably predict exposure-response relationships, immunogenicity of different forms of beryllium, or mechanisms relevant to human CBD.

Generally, more soluble forms of beryllium, such as beryllium salts as opposed to beryllium metal, have shorter half-lives in the lung and a greater potential for systemic absorption and sensitization; relatively insoluble forms of inhaled beryllium (beryllium metal and beryllium oxide) deposited in the lungs will be retained with much longer half-lives and may lead to sensitivity reactions or toxicity even after a single exposure. No animal model has characteristics of human CBD that are sufficient for it to be used to establish the relative importance of the various chemical forms (including alloys) or physical characteristics of inhaled beryllium encountered in the workplace.

The mechanism underlying CBD pathogenesis involves an antigenic immune response to beryllium associated with beryllium-specific $CD4^+$ T cells. Progress has made in characterizing the immune response to beryllium and host risk factors. More research is needed on the nature of the beryllium antigen recognized by the $CD4^+$ T cells.

Research has also indicated that an allele of HLA-DPβGlu69 is the most important marker of susceptibility to CBD. However, the presence of that marker alone does not necessarily confer susceptibility, nor is its absence a guarantee of nonsusceptibility. T-cell–receptor expression,

inflammation-related genes, and other potential modifier genes also appear to play roles in disease progression and warrant further investigation.

Efforts are under way to create humanized-mouse models in which human alleles are associated with a range of BeS and CBD risk that might be useful in experimental study of beryllium dose-response relationships, of beryllium types and characteristics that confer risk, and of therapeutic approaches to beryllium diseases. It is unclear whether expression of single target genes associated with sensitization will recapitulate the signs and symptoms of human CBD. There is no doubt that an animal model of immune-mediated CBD as it occurs in humans would aid substantially in developing an understanding of the mechanisms of CBD and the relative importance of the various forms of beryllium encountered in the workplace in the causation of CBD.

5

Genotoxicity and Carcinogenicity

The carcinogenic potential of beryllium and beryllium compounds has been assessed by various agencies in the last decade. The International Agency for Research on Cancer (IARC 1993) classifies beryllium and beryllium compounds as carcinogenic in humans, the U.S. Environmental Protection Agency (EPA 1998a,b) considers them probable human carcinogens, and the National Toxicology Program (NTP 1999, 2005) lists them as reasonably expected to be carcinogens. As noted in Chapter 1, EPA has performed a dose-response analysis of the cancer data to estimate an inhalation unit risk of 2.4 $\times 10^{-3}$ per $\mu g/m^3$. This chapter examines the literature used in the previous assessments, more recent reviews, and relevant new studies. Information on the genotoxic potential of beryllium and beryllium compounds is presented first, and then the literature on carcinogenicity, including the epidemiologic literature and animal bioassays, is reviewed.

GENOTOXICITY

Compounds of beryllium have tested positive in nearly 50% of the genotoxicity studies conducted without exogenous metabolic activation but were nongenotoxic in most bacterial tests. Beryllium chloride, beryllium nitrate, beryllium sulfate, and beryllium oxide have been shown to be nongenotoxic in the Ames plate incorporation assay and assays with *Escherichia coli pol A*, *E. coli* WP-2 *uvr A*, and *Saccharomyces cerevisiae* (Table 5-1) (reviewed in EPA 1998a,b; ATSDR 2002; Gordon and Bowser 2003). Beryllium sulfate also did not induce unscheduled DNA synthesis in primary rat hepatocytes (Williams et al. 1982, 1989), was not mutagenic when injected intraperitoneally into adult mice in a *Salmonella typhimurium* host-mediated assay (Simmon et al. 1979), and failed to increase the incidence of micronucleated polychromatic erythrocytes in bone marrow (Ashby et al.1990). Lung tumors in F344/N rats treated with beryllium sulfate did not have mutations of the *p53* or *c-raf*-1 gene, but weak mutations were detected in the K-*ras* gene (Nickell-Brady et al. 1994).

Positive genotoxic results have been reported with beryllium sulfate in the *Bacillus subtilis* rec assay (Kada et al. 1980; Kanematsu et al. 1980) and the *E. coli* rec assay (Dylevoi 1990), with beryllium nitrate in the *B. subtilis* rec assay (Kuroda et al. 1991), and with beryllium chloride in the *B. subtilis* rec assay with spores (Kuroda et al. 1991), the *E. coli* forward-mutation assay (Zakour and Glickman 1984), and the *Photobacterium fischeri* assay (Ulitzur and Barak 1988). Gene mutations have been observed in mammalian cells cultured with beryllium chloride (Vegni-Talluri and Guiggiani 1967; Hsie et al. 1979; Miyaki et al. 1979) and beryllium sulfate (Larramendy et al. 1981; Brooks et al. 1989); beryllium nitrate has resulted in clastogenic alterations (Kuroda et al. 1991). Overall, mutation and chromosomal-aberration assays of beryllium compounds have yielded somewhat contradictory results. Although the bacterial assays have been largely negative, the mammalian test systems exposed to beryllium compounds have shown evidence of mutations, chromosomal aberrations, and cell transformations. However, results of the mammalian test systems have also been inconsistent. The chemical form of beryllium does not appear to determine genotoxic results (Table 5-1). Further studies would confirm the mutagenic or genotoxic properties of the various beryllium compounds.

TABLE 5-1 Genotoxicity Studies of Beryllium Compounds

Assay or End Point	Species	Compound	With Activation	Without Activation	Reference
In vitro					
Plate incorporation assay	*Salmonella typhimurium*	$BeSO_4$	Negative	Negative	Rosenkranz and Poirier 1979; Simmon 1979a; Simmon et al. 1979; Dunkel et al. 1984; Arlauskas et al. 1985; Ashby et al. 1990
	S. typhimurium	$Be(NO_3)_2$	Negative	Negative	Arlauskas et al. 1985; Kuroda et al. 1991
	S. typhimurium	BeO	Negative	Negative	Kuroda et al. 1991
	S. typhimurium	$BeCl_2$	Negative	Negative	Kuroda et al. 1991
	Eschericia coli WP-2 *uvrA*	$BeSO_4$	Negative	Negative	Dunkel et al. 1984
Rec assay	*Bacillus subtilis*	$BeSO_4$	—	Positive	Kada et al. 1980; Kanematsu et al. 1980
	B. subtilis	$BeCl_2$	—	Positive	Kuroda et al. 1991
	B. subtilis	$BeCl_2$	—	Negative	Nishioka 1975
	B. subtilis	$Be(N0_3)_2$	—	Positive	Kuroda et al. 1991
	B. subtilis	BeO	—	Negative	Kuroda et al. 1991
	E. coli	$BeSO_4$	—	Positive	Dylevoi 1990
DNA modification	*E. coli pol* A^+/A^-	$BeSO_4$	—	Negative	Rosenkranz and Poirier 1979
Bioluminescence test	*Photobacterium fischeri*	$BeCl_2$	—	Positive	Ulitzur and Barak 1988
Recombogenic activity	*Saccharomyces cerevisiae*	$BeSO_4$	Negative	Negative	Simmon 1979b
Host-mediated assay	*S. cerevisiae*	$BeSO_4$	—	Negative	Simmon et al. 1979
	S. typhimurium	$BeSO_4$	—	Negative	Simmon et al. 1979
Chromosomal aberration	Swine lymphocytes	$BeCl_2$	—	Positive	Vegni-Talluri and Guiggiani 1967
	Syrian hamster embryo cells	$BeSO_4$	—	Positive	Larramendy et al. 1981
	Human lymphocytes	$BeSO_4$	—	Positive	Larramendy et al. 1981
	Chinese hamster ovary cells	$BeSO_4$	—	Negative	Brooks et al. 1989
Cytogenetic assay	Chinese hamster lung cells	$BeSO_4$	Negative	Negative	Ashby et al. 1990
Sister-chromatid exchange assay	Chinese hamster V79 cells	$BeCl_2$	—	Positive	Kuroda et al. 1991
	Chinese hamster V79 cells	$Be(NO_3)_2$	—	Positive	Kuroda et al. 1991
	Chinese hamster V79 cells	BeO	—	Negative	Kuroda et al. 1991
	Syrian hamster embryo cells	$BeSO_4$	—	Positive	Larramendy et al. 1981
	Human lymphocytes	$BeSO_4$	—	Positive	Larramendy et al. 1981
	Human lymphocytes	$BeSO_4$	—	Negative	Andersen 1983

(Continued)

TABLE 5-1 Continued

Assay or End Point	Species	Compound	With Activation	Without Activation	Reference
	Mouse macrophage $P388D_1$ cells	$BeSO_4$	—	Negative	Andersen 1983
DNA repair	Rat hepatocytes	$BeSO_4$	—	Negative	Williams et al. 1982, 1989
Transformation assay	Syrian hamster embryo cells	$BeSO_4$	—	Positive	DiPaolo and Casto 1979
	Rat respiratory epithelial cells	Rocket-exhaust residue	—	Mixed	Steele et al. 1989
	Rat respiratory epithelial cells	BeO (low-fired)	—	Positive	Steele et al. 1989
	Rat respiratory epithelial cells	BeO (high-fired)	—	Mixed	Steele et al. 1989
	BALB/c-3T3 cells	$BeSO_4$	—	Positive	Keshava et al. 2001
DNA damage	Rat respiratory epithelial cells	Rocket-exhaust residue	—	Mixed	Steele et al. 1989
	Rat respiratory epithelial cells	BeO (low-fired)	—	Positive	Steele et al. 1989
	Rat respiratory epithelial cells	BeO (high-fired)	—	Mixed	Steele et al. 1989
Mutation of HGPRT gene	Chinese hamster ovary K_1-BH_4 cells	$BeSO_4$	—	Positive	Hsie et al. 1979
	Chinese hamster V79 cells	$BeCl_2$	—	Positive	Miyaki et al. 1979
Mutation of *lacI* gene	*E. coli*	$BeCl_2$	—	Positive	Zakour and Glickman 1984
Mutation of K-*ras* gene	Rat lung tumors	Be	—	Weak positive	Nickell-Brady et al. 1994
Mutation of *p53* gene	Rat lung tumors	Be	—	Negative	Nickell-Brady et al. 1994
Mutation of c-*raf*-1 gene	Rat lung tumors	Be	—	Negative	Nickell-Brady et al. 1994
In vivo					
Transformation assay	Syrian hamsters (embryo cells evaluated after maternal exposure)	$BeSO_4$	—	Positive	DiPaolo and Casto 1979
Micronucleus assay	CBA mice	$BeSO_4$	—	Negative	Ashby et al. 1990

ABBREVIATIONS: Be, beryllium; $BeCl_2$, beryllium chloride; $Be(NO_3)_2$, beryllium nitrate; BeO, beryllium oxide; $BeSO_4$, beryllium sulfate.
Source: Adapted from ATSDR 2002.

CARCINOGENICITY

Epidemiologic Studies

Several studies and reviews on cancer in relation to human exposure to beryllium are available. Two worker cohorts involved in beryllium extraction, production, and fabrication have been extensively

studied and have been the primary basis of conclusions drawn on cancer in humans. One cohort was in Lorain, Ohio, and the other in Reading, Pennsylvania. The original study (Mancuso 1979) reported a lung-cancer standardized mortality ratio (SMR) in the two plants combined of 1.42 (95% confidence interval [CI], 1.1-1.8). The study involved 1,222 workers at the Ohio plant and 2,044 workers at the Pennsylvania plant who had been employed for at least 3 months during 1942-1948. No analysis by job title or by exposure category was performed, and the excess–lung-cancer finding was limited to workers who were employed for less than 5 years. Worker exposure was often at high concentration. For example, a study at the Ohio plant in 1947-1948 by the U.S. Atomic Energy Commission measured beryllium at concentrations ranging from 411 $\mu g/m^3$ in the mixing area to 43,300 $\mu g/m^3$ in the breathing zone of alloy operators (Zielinski 1961). Control limits at U.S. plants were introduced in 1949 (Wagoner et al. 1980). Mancuso (1980) reanalyzed the same two cohorts but expanded the period of employment of the study cohorts to 1937-1948 and used workers at a rayon plant for comparison purposes. The comparison between the two types of industrial workers found a significant relative lung-cancer SMR of 1.40 for the beryllium-worker cohort.

Wagoner et al. (1980) expanded the cohort in the Pennsylvania plant to include workers employed during 1941-1967. The group of 3,055 workers was found to have a lung-cancer SMR of 1.25 (95% CI, 0.9-1.7). When the analysis was adjusted for latency, there was a significant SMR of 1.68 in the group that had a latency of 25 years or longer, but there was no relationship with duration of employment. The results of a 1968 medical survey of smoking histories of the workers showed that smoking increased the cancer risk in beryllium workers by 14%. However, if the working population's risk is compared with lung-cancer mortality in the county where the plant was instead of using the U.S. rates, the SMR is underestimated by 19% (Wagoner et al. 1980).

The National Institute for Occupational Safety and Health (NIOSH) conducted a retrospective cohort mortality study of seven beryllium-production facilities that included the Pennsylvania and Ohio cohorts previously studied by Mancuso and Wagoner. Ward et al. (1992) developed a cohort of 9,225 male workers who had worked for at least 2 days during 1940-1969 and were followed through 1988. The lung-cancer SMR was 1.26 (95% CI, 1.12-1.42) on the basis of 280 lung-cancer deaths. The researchers also observed an SMR for nonmalignant respiratory disease of 1.48 (95% CI, 1.21-1.80). Ward et al. (1992) reported that SMR increased with latent period: there was a significant SMR of 1.46 for a latent period greater than 30 years in the workers at the combined seven plants. The lung-cancer SMR was a significant 1.42 in those hired before 1950 and was less than l in those hired during 1960 through 1969.

IARC (1993) has provided a detailed description and critique of the cohort studies. It pointed out that the risk of lung cancer was consistently higher in plants in which there was excess mortality from nonmalignant respiratory disease. IARC also concluded that the association between lung-cancer risk and beryllium exposure did not appear to be confounded by smoking.

A second line of investigation is embodied in the Beryllium Case Registry, which was established in 1952 to follow the clinical aspects of and complications in beryllium-related diseases, including chronic beryllium disease (CBD) and acute beryllium-related pneumonitis. The data were analyzed first by Infante et al. (1980) and more recently by Steenland and Ward (1991). In the Steenland and Ward study, the cohort consisted of 689 people who entered the registry during 1952-1980 and were followed through 1988. The researchers reported an SMR of 2.00 (95% CI, 1.33-2.89) on the basis of 28 observed lung-cancer deaths. The lung-cancer SMR was greater in people who had acute beryllium pneumonitis (SMR, 2.32) than in those who had CBD (SMR, 1.57); the former was statistically significant. IARC (1993) concluded that the studies of cases in the Beryllium Case Registry provided indirect evidence that beryllium, rather than smoking, explained the increase in lung cancer on the grounds of the assumption that people with acute pneumonitis were unlikely to smoke more than workers with CBD.

With respect to other cancer end points, Carpenter et al. (1988) conducted a nested case-control study of cancers of the central nervous system in workers at facilities in Oak Ridge, Tennessee. There were 72 male and 17 female deaths due to central-nervous-system cancer. Using job titles, the investigators considered the potential exposure to each of 26 chemicals, including beryllium. There was a weak association with exposure to beryllium (odds ratio, 1.5; 95% CI, 0.6-3.9). The authors concluded

that their study did not support the hypothesis that occupational exposure to the chemicals they studied increased the risk of cancer of the central nervous system appreciably. IARC (1993) noted that the risk of cancer of the central nervous system increased with longer duration of employment in jobs with greater exposure to beryllium.

On the basis of the studies described above, IARC concluded that there is *sufficient evidence* of the carcinogenicity of beryllium and beryllium compounds in humans. That conclusion was based on the cohort studies, which showed

- A large number of lung-cancer cases with a stable estimate of the SMR.
- Consistency among locations.
- A greater excess of lung cancer among workers hired before 1950, when exposure was greater.
- The highest lung-cancer risk at the plant that had the greatest proportion of acute beryllium-pneumonitis cases in the Beryllium Case Registry.
- High lung-cancer risks at plants with the greatest risk of pneumoconiosis and other respiratory diseases.
- A greater lung-cancer risk in the Beryllium Case Registry cohort.
- Increasing risk with longer latency.

IARC pointed out the following limitations:

- Absence of individual exposure measurements.
- Relatively low excess lung-cancer risk.
- Absence of any mention of exposure to other lung carcinogens in the workplace.

A series of letters and papers issued after the IARC report raised concerns about and objections to the basis of its conclusions. Some raised concerns about the IARC procedures, the information available to the IARC working group, and possible conflicts of interest (Kotin 1994a,b; Vainio and Kleihues 1994). Others questioned the validity of the Ward et al. study. Questions were raised about the dataset used to estimate background lung-cancer rates, how to combine data from multiple plants, and how to adjust for cigarette-smoking (MacMahon 1994; Levy et al. 2002). Levy et al. (2002) have reported that alternative adjustments and comparisons to address those issues left no statistical association between beryllium exposure in the workers and lung cancer.

Since the IARC evaluation in 1993, there have been two additional studies. Sanderson et al. (2001b) conducted a nested case-control study of plant workers at the Reading, Pennsylvania, facility. The cohort of 3,569 male workers was the same as the cohort in the 1992 Ward et al. study. The lung-cancer cases numbered 142 on the basis of a followup of the cohort through 1992, and each was age- and race-matched to five controls. In addition to assessment of beryllium exposure, the potential for confounding by smoking was evaluated. The cases had lower lifetime exposure to beryllium. However, when a 10-year lag and a 20-year lag were applied, the exposure metrics were higher in cases. Furthermore, significant positive trends in the log of exposure metrics were observed, and the authors concluded that smoking did not confound the exposure-response analysis.

Methodologic concerns have been raised about the Sanderson et al. study (Deubner et al. 2001c, 2007; Levy et al. 2007). The principal objection concerned the potential for confounding by birth year or age at hire, neither of which had been explicitly considered by Sanderson et al. In response, Schubauer-Berigan et al. (2008) reanalyzed the Sanderson et al. study and investigated potential confounding and effect modification by birth year (which was highly correlated with age at hire). They also assessed the sensitivity of the exposure-risk association to a small but potentially important methodologic choice: using a small value as a "start" when taking the logarithm of exposure metrics to avoid taking the logarithm of zero. The Schubauer-Berigan et al. reanalysis confirmed a significant association between beryllium exposure and lung-cancer risk, although the exposure metric and time lag that revealed the

strongest evidence differed from those in the original study. Sanderson et al. reported an association between cumulative exposure with a latency of 20 years, whereas Schubauer-Berigan et al. found the beryllium–lung-cancer association when using average exposure with a 10-year latency. Changing the "start" value that was used in lagging exposure metrics did not substantially affect the results.

Brown et al. (2004) conducted a nested case-control study of lung cancer in a cohort of plutonium-exposed workers at Rocky Flats. The main focus of the study was on the risk posed by plutonium, but an attempt was also made to assess risks associated with asbestos, hexavalent chromium, nickel, and beryllium. The 120 cases of primary lung cancer identified from death certificates and a tumor registry were matched to 720 controls. There was evidence of increased lung-cancer risk with increasing plutonium dose. Beryllium exposure was estimated with a job-exposure matrix, but no details were provided in the paper. The authors reported that cumulative exposure to beryllium was not "significantly associated" with lung-cancer risk, but no details or results were presented. Their paper provides only limited evidence bearing on the question of beryllium carcinogenicity in that no quantitative results were presented.

NIOSH is conducting a new retrospective cohort study of the principal U.S. beryllium-production facilities, including a detailed exposure reconstruction. The study should provide considerably stronger findings on human lung-cancer risk than the existing studies.

Animal Studies

This section focuses on studies of inhalation exposure to beryllium and its compounds and the later development of neoplasms in laboratory animals (see Table 5-2). Lung neoplasms have been found in rats and monkeys exposed to beryllium compounds by inhalation.

Albino Sherman and Wistar rats (male and female) were exposed by inhalation to an aqueous aerosol of beryllium sulfate tetrahydrate (which contained beryllium at 35.7 $\mu g/m^3$) 8 hours/day, 5.5 days/week, for 6 months (Schepers et al. 1957). The rats were observed for 18 months after exposure. Lung neoplasms (18 adenomas, five squamous-cell carcinomas, 11 papillary adenocarcinomas, and seven alveolar-cell adenocarcinomas) were observed in the treated rats but not in the control rats.

A study by Vorwald and Reeves (1959) reported the development of lung neoplasms in Sherman rats (number and sex not reported) exposed by inhalation to beryllium sulfate at 6 and 54.7 $\mu g/m^3$ 6 hours/day, 5 days/week, for up to 18 months. The neoplasms observed were primarily adenomas and squamous-cell cancers.

A study by Reeves et al. (1967) exposed male and female Sprague-Dawley rats to beryllium sulfate at 34.25 $\mu g/m^3$ 7 hours/day, 5 days/week. The mean particle size of the beryllium sulfate aerosol was 0.118 μm. Exposure lasted up to 72 weeks. After 13 months of exposure, all the exposed rats had developed alveolar adenocarcinomas; the control rats had no lung neoplasms. The neoplasia was preceded by a proliferative response that progressed from hyperplasia to neoplasia.

In another study in which particle size was calibrated, Charles River CD rats were exposed to beryllium sulfate at 35.16 $\mu g /m^3$, with a mean particle size of 0.21 μm, 35 hours/week (Reeves and Deitch 1969). Exposure duration was 800, 1,600, and 2,400 hours. The lung- tumor incidence in young rats exposed for 3 months (86%, 19 of 22 rats) was the same as that in older rats exposed for 18 months (87%, 13 of 15 rats). However, older rats that were exposed to beryllium sulfate for 3 months had fewer lung neoplasms than rats that were exposed when they were younger. The pulmonary neoplasms were typically observed after a latency of 9 months. Preneoplastic lesions were described as epithelial hyperplasia at 1 month, metaplasia at 5-6 months, and anaplasia at 7-8 months.

Male and female rhesus monkeys (*Macaca mulatta*) were exposed to beryllium sulfate at 35 $\mu g/m^3$ 6 hours/day, 5 days/week (Vorwald 1968). Exposure was often interrupted for considerable periods to prevent the monkeys from developing acute beryllium pneumonitis (four monkeys died of acute chemical pneumonitis during the first 2 months of the study). The longest exposure was for a total of

TABLE 5-2 Inhalation-Carcinogenicity Studies of Beryllium

Reference	Species	Route	Dose	Findings
Acute exposure				
Sanders et al. 1978	Rat	Inhalation	1.0-91 μg of Be from BeO (single alveolar deposition); particle size, 1.10 ± 0.17 μm (GSD, 2.17 ± 0.17 μm)	Alveolar half-life of Be in lungs, 325 days; 1 of 184 rats had lung tumors after 2 years
Groth et al. 1980	Rat	Intratracheal	Be at 0.5, 2.5 mg/m^3 as passivated metal (Be-Cr), alloys (Al, Cu, Ni, Cu-Co); particle size, 1-2 μm	Lung adenomas, adenocarcinomas found in 2 of 21, 9 of 16 treated with Be; 7 of 20. 9 of 26 treated with Be-Cr; 1 of 21, 4 of 24 treated with Be-Al, respectively; no tumors with other alloys
Litvinov et al. 1983	Rat	Intratracheal	BeO at 0.036, 0.36, 3.6, 18 mg/kg (low- and high-fired)	Malignant epithelial lung tumors after low-fired BeO, 0 of 76, 0 of 84, 2 of 77, 2 of 103, respectively; after high-fired BeO, 3 of 69, 7 of 81, 18 of 79, 8 of 26, respectively
Nickell-Brady et al. 1994	Rat	Inhalation	Be at 410, 500, 830, 980 mg/m^3 (single exposure; lung burdens, 110, 40, 360, 430 μg); particle size, 1.4 μm (GSD, 1.9 μm)	64% of rats developed lung tumors (primarily adenocarcinomas) after 14 months
Short-term and subchronic exposure				
Vorwald and Reeves 1959	Rat	Intratracheal	4.5 mg of Be as BeO, 0.1071 mg of Be as $BeSO_4$ (three injections over 3 weeks)	Lung tumors began to appear after 8 months; percentage of rats affected not specified
Ishinishi et al. 1980	Rat	Intratracheal	1 mg of BeO (low-fired) (once a week for 15 weeks)	1 adenocarcinoma, 1 squamous-cell carcinoma, 4 adenomas
Chronic exposure				
Dutra et al. 1951	Rabbit	Inhalation	BeO at 1, 6, 30 μg/L (5 hours/day, 5 days/week, 9-13 months); particle size, 0.285 μm (mean), 0.11-1.25 μm (range)	6 of 9 rabbits developed osteosarcomas after 1 year
Schepers et al. 1957	Rat	Inhalation	Be at 35.7 μg/m^3 as $BeSO_4$ (8 hours/day, 5.5 days/week, up to 6 months)	Lung-cancer rates higher in exposed rats than in controls
Vorwald and Reeves 1959	Rat	Inhalation	Be at 0.0547 mg/m^3 as $BeSO_4$, at 0.006 mg/m^3 as BeO (6 hours/day, 5 days/week, various durations up to 18 months)	Lung tumors began to appear after 9 months; percentage of rats affected not specified, but later report (Vorwald et al. 1966) described incidence of cancer as "almost 100%" in "large number" of surviving rats
Reeves et al. 1967	Rat	Inhalation	Be at 34.25 μg/m^3 (mean) as $BeSO_4$ (7 hours/day, 5 days/week, 72 weeks); particle size, 0.118 μm	All rats developed lung tumors (adenocarcinomas) by 13 months
Vorwald 1968	Monkey	Inhalation	$BeSO_4$ at 35 μg/m^3 (6 hours/day, 5 days/week, various interruptions, variable durations up to 4,070 hours)	8 of 12 monkeys had pulmonary anaplastic carcinomas (adenomatous, epidermoid patterns); first tumor observed after 3,241 hours of exposure

Reeves and Deitch 1969	Rat	Inhalation	$BeSO_4$ at 35.16 µg/m^3 (35 hours/week for 800, 1,600, 2,400 hours); particle size, 0.21 µm (mean)	19 of 22 young rats, 13 of 15 older rats developed lung tumors after 3 and 18 months, respectively; at 3 months, older rats had fewer lung neoplasms than younger rats
Wagner et al. 1969	Rat, hamster, squirrel monkey	Inhalation	Bertrandite dust at 15 mg/m^3 (Be at 210 µg/m^3), beryl ore at 15 mg/m^3 (Be at 620 µg/m^3) (6 hours/day, 5 days/week, up to 23 months); particle size, bertrandite, 0.27 µm (mean); beryl ore, 0.64 µm (mean)	18 of 19 rats exposed to beryl ore had lung tumors (bronchial alveolar-cell tumors, adenomas, adenocarcinomas, epidermoid tumors); no increased incidence of tumors in rats from dust or in other species from either compound
Litvinov et al. 1975	Rat	Inhalation	BeF_2 at 0.04, 0.4 mg/m^3, $BeCl_2$ at 0.02, 0.2 mg/m^3 (1 hour/day, 5 days/week, 4 months)	Lung tumors found in treatment groups
Litvinov et al. 1984	Rat	Inhalation	BeO, $BeCl_2$ at 0.8, 4, 30, 400 µg/m^3 (1 hour/day, 5 days/week, 4 months)	Malignant lung tumors found in 3 of 44, 4 of 39, 6 of 26, 8 of 21 in BeO group and 1 of 44, 2 of 42, 8 of 24, 11 of 19 in $BeCl_2$ group, respectively
Finch et al. 1998b	Mouse (*p53*$^{+/-}$ knockout and *p53*$^{+/+}$ wild- type)	Inhalation	15, 60 µg of Be (60 µg achieved over 3 days); particle size, 1.4 µm (mean) (GSD, 1.8 µm)	4 of 28 *p53*$^{+/-}$ mice in high-dose group developed lung tumors; no lung tumors in low-dose group or in *p53*$^{+/-}$ mice
Mode-of-action studies				
Skilleter et al. 1991	Rat hepatic BL9L cells	In vitro	50 µM $BeSO_4$	$BeSO_4$ inhibited cell division during G1 phase of cell cycle, but expression of c-*myc* was maintained in serum-stimulated cells
Nickell-Brady et al. 1994	Rat	Inhalation	Be at 410, 500, 830, 980 mg/m^3 (single exposure; lung burdens, 40, 110, 360, 430 µg); particle size, 1.4 µm (GSD, 1.9 µm)	Analysis of *p53* and c-*raf*-1 genes in neoplasms did not indicate genetic alterations; weak evidence of mutation of K-*ras* gene
Swafford et al. 1997	Rat primary lung tumors, cell lines from Nickell-Brady et al. (1994) study			Aberrant methylation status of *p16*^{INK4a} , leading to loss of expression
Joseph et al. 2001	Mouse BALB/c-3T3 cells	Transformed cells injected into nude mice, cell lines derived from resulting tumors	$BeSO_4$ at 50-200 µg/mL	Analyses of gene expression indicate that cell transformation and tumorigenesis are associated with upregulated expression of genes related to cancer (such as c-*fos*, c-*jun*, c-*myc*, R-*ras*) and downregulated expression of genes involved in DNA synthesis, repair, recombination (such as *MCM4*, *MCM5*, *PMS2*, *Rad23*, DNA ligase I)

(Continued)

TABLE 5-2 Continued

Reference	Species	Route	Dose	Findings
Keshava et al. 2001	Mouse BALB/c-3T3 cells	In vitro	$BeSO_4$ at 50-200 µg/mL	Results show that cells transformed by $BeSO_4$ are potentially tumorigenic; transformation might involve gene amplification of K-*ras*, c-*jun;* some transformed cells have neoplastic potential because of genomic instability
Belinsky et al. 2002	Rat	Inhalation	40, 110, 360, 430 µg of Be (single dose; mean lung burdens)	Tumors induced in part through inactivation of p16 and ER genes
Misra et al. 2002	Mouse peritoneal macrophages	In vitro	1-5 nM BeF_2	Phosphorylation increased kinases MEK1, ERK1, p38 MAPK, JNK; increases also seen in NF-κB, CREB transcription factors, c-*fos*, c-*myc*

ABBREVIATIONS: Al, aluminum; Be, beryllium; $BeCl_2$, beryllium chloride; BeF_2, beryllium fluoride; BeO, beryllium oxide; $BeSO_4$, beryllium sulfate; Co, cobalt; Cr, chromium; Cu, copper; GSD, geometric standard deviation; Ni, nickel.

4,070 hours, and most of the exposure periods occurred during the first 4.5 years of the study. A 6-month exposure occurred 2.5 years after the initial 4.5-year exposure period. The authors reported that pulmonary anaplastic carcinomas (adenomatous and epidermoid patterns) were observed in eight of 12 monkeys; the first tumor was in a monkey that had been exposed for 3,241 hours. The neoplasms metastasized to mediastinal lymph nodes and other areas of the body.

Lung tumors were observed in male white random-bred rats exposed to beryllium fluoride (at 0.4 and 0.04 mg/m^3) or beryllium chloride (at 0.2 and 0.02 mg/m^3) 1 hour/day, 5 days/week, for 4 months (Litvinov et al. 1975). The first neoplasms were observed after 16 months in rats exposed to beryllium fluoride at 0.4 mg/m^3 and beryllium chloride at 0.2 mg/m^3. Neoplasms also developed in the lungs of rats exposed at the lower concentrations but not in the lungs of the control rats.

Litvinov et al. (1984) exposed female albino rats to beryllium oxide or beryllium chloride at 0.8, 4, 30, and 400 μg/m^3 1 hour/day, 5 days/week, for 4 months. Malignant lung neoplasms developed in a dose-related manner after exposure to either beryllium oxide or beryllium chloride but were not found in the controls.

The carcinogenicity of two beryllium ores, bertrandite and beryl, was evaluated in male squirrel monkeys (*Saimiri sciurea*), male Charles River-CD rats, male Greenacres Controlled Flora (GA) rats, and male Golden Syrian hamsters (Wagner et al. 1969). The rats and hamsters were exposed to bertrandite or beryl at 15 mg/m^3 6 hours/day, 5 days/week, for 17 months, and the monkeys were exposed for 23 months. Beryllium from bertrandite was present in the test atmospheres at 210 μg/m^3 and from beryl at 620 μg/m^3; the geometric mean diameters of the particles were 0.27 μm and 0.64 μm, respectively. In the beryl-exposed rats, squamous metaplasia or small epidermoid tumors were identified in the lungs of five of 11 rats killed after 12 months of exposure and in 18 of 19 rats after 17 months of exposure. Eighteen of the rats had bronchiolar alveolar-cell tumors, nine had adenocarcinomas, seven had adenomas, and four had epidermoid tumors. Although granulomatous lesions were observed in the bertrandite-exposed rats, no neoplasms were identified in the rats exposed for 6, 12, or 17 months. Neither neoplasms nor granulomas developed in the control rats.

Atypical proliferations were observed in the lungs of hamsters 12 months after exposure to bertrandite or beryl. The lesions were reported to be larger and more adenomatous in the beryl group after 17 months. No pulmonary lesions occurred in the control hamsters. No tumors were observed in either the bertrandite- or beryl-treated monkeys.

The carcinogenicity of beryllium metal has also been investigated. In one study, male and female F344/N rats received a single, nose-only exposure to a beryllium-metal aerosol at 500 mg/m^3 for 8 minutes, at 410 mg/m^3 for 30 minutes, at 830 mg/m^3 for 48 minutes, or at 980 mg/m^3 for 39 minutes (Nickell-Brady et al. 1994). The latent period for development of neoplasms was about 14 months; tumor incidence was 64% over the lifetime of the rats. Most of the neoplasms were adenocarcinomas, although multiple tumor types were observed.

In another study of beryllium metals (Groth et al. 1980), lung adenomas and adenocarcinomas were observed in nine of 16 female Wistar rats that received a single intratracheal instillation of 2.5 mg of beryllium metal, nine of 26 rats treated with 2.5 mg of passivated beryllium metal, and four of 24 rats given 2.5 mg of beryllium-aluminum alloy. No neoplasms were observed in the lungs of the controls.

Pulmonary neoplasms developed in inbred albino rats that were given single intratracheal deposits of beryllium oxide (fired at high and low temperatures) at 0.036, 0.36, 3.6, or 18 mg/kg (Litvinov et al. 1983). The neoplasms were adenomas, adenocarcinomas, and squamous-cell carcinomas.

Wistar rats received intratracheal instillations of 1 mg of beryllium oxide (low-fired) once a week for 15 weeks (Ishinishi et al. 1980). An adenocarcinoma, a squamous-cell carcinoma, and four adenomas were observed in the lungs of 30 beryllium-treated rats and no neoplasms in the 16 controls.

The mechanism by which beryllium induces carcinogenesis remains unknown. Analysis of *p53* and c-*raf*-1 genes in neoplasms did not indicate genetic alterations, although there was weak evidence of mutations of the k-*ras* gene (Table 5-2) (Nickell-Brady et al. 1994). It has been suggested that cell transformation and tumorigenesis are associated with upregulated expression of c-*fos*, c-*jun*, c-*myc*, and R-*ras* genes and downregulation of such genes as *MCM4*, *MCM5*, *PMS2*, *Rad23*, and DNA ligase I

(Joseph et al. 2001). Others have reported that transformation by beryllium might involve amplification of k-*ras* and c-*jun* (Keshava et al. 2001). Peritoneal macrophages exposed to beryllium showed increased phosphorylation for several kinases and increases in NF-κB, CREB transcription factors, c-*fos*, and c-*myc* (Misra et al. 2002). Additional studies are warranted to improve understanding of the mechanisms by which beryllium induces pulmonary neoplasms in animals.

In summary, beryllium compounds have induced pulmonary neoplasms in seven strains of rats and the rhesus monkey. Forms of beryllium that have induced neoplasia in animals are beryllium sulfate, beryllium fluoride, beryllium chloride, beryllium oxide, the beryllium ore beryl, and beryllium metals. The types of pulmonary neoplasms reported after exposure included adenomas, adenocarcinomas, papillary adenocarcinomas, alveolar-cell adenocarcinomas, bronchiolar alveolar-cell tumors, epidermoid tumors, and squamous-cell carcinomas. Lung tumors have also been induced by beryllium in p53+/- knockout mice. Results of genotoxicity studies show no consistency in type of beryllium tested or genotoxic assay performed.

Cancer Risk Estimates

EPA (1998a,b) classifies beryllium as a likely human carcinogen on the basis of epidemiologic studies that found increases in lung cancer and supporting evidence from animal studies that beryllium induces lung cancer in rats and monkeys. For carcinogens, EPA calculates an inhalation unit risk, which is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$. For beryllium, the unit risk is estimated to be 2.4×10^{-3}. The cancer dose-response assessment for that estimate was originally performed in 1987 and based on an occupational-exposure study (Wagoner et al. 1980). For its cancer-risk estimation, EPA had to assume an occupational exposure of 100 mg/m^3 or 1,000 mg/m^3. Dose-response assessments from animal studies yielded similar estimates of risk, but EPA considered epidemiologic data to be a better basis for estimating cancer risks. In 1998, EPA noted that new epidemiologic studies had been published but found that they shared the same limitations as the Wagoner et al. (1980) study in lacking individual exposure monitoring or job-history data to support a better quantitative dose-response assessment. However, EPA also noted that a NIOSH study that was being published appeared to have exposure data that might be suitable for quantitative estimation. Until those data were published, EPA recommended that its original unit risk of 2.4×10^{-3} be retained. On the basis of that value, EPA estimated that air concentrations of 0.04, 0.004, and 0.0004 $\mu g/m^3$ would result in cancer risks of 1×10^{-4}, 1×10^{-5}, and 1×10^{-6}, respectively. The NIOSH study was published in 2001 (Sanderson et al. 2001b); EPA is reassessing beryllium cancer risks.

In reviewing the lung-cancer case-control study by Sanderson et al. (2001b) and the reanalyses by Levy et al. (2007) and Schubauer-Berigan et al. (2008), the committee questioned whether a quantitative cancer risk assessment could be carried out with these data. The key reasons for the question were the following:

- Three dose metrics were used (cumulative exposure, average exposure, and maximum exposure). The increased odds ratios were associated only with average and maximum exposure, and this suggests that if beryllium induces lung cancer, it may be a high-dose effect.
- The odds ratios were approximately constant over the quartiles except for the lowest quartile. That makes it problematic in fitting any dose-response model that is intended to estimate low-dose effects.

CONCLUSIONS AND RECOMMENDATIONS

There is evidence from controlled studies that exposure to beryllium can cause lung cancer in both sexes of rats, and one study reported lung tumors in monkeys. Epidemiologic studies have reported

increases in lung-cancer risk in two worker cohorts exposed to beryllium. Those studies were instrumental in forming the basis of the current cancer classifications by such agencies as IARC, EPA, and NTP. New studies and reanalyses of data performed since those assessments have not added substantially to understanding of the carcinogenicity of beryllium or of a dose-response relationship between exposure to beryllium and the development of lung cancer. The committee agrees with the other agencies that the balance of the evidence supports a conclusion that beryllium is likely to be a human carcinogen.

The committee was charged with developing carcinogenic risk estimates for different magnitudes of inhalation exposure to beryllium. However, the committee judged that the available human and animal data are inadequate to support a dose-response analysis with low-dose extrapolation to current exposure level magnitudes. Several critical questions needed to characterize a dose-response relationship cannot be answered now. Those questions include

- What physicochemical characteristics and particle sizes are associated with beryllium-induced cancer?
- Is cancer risk driven by peak exposures, by cumulative exposures, or by other dose metrics?
- How have earlier and later exposures of beryllium workers to other lung carcinogens affected disease incidence?
- How have changes in workplace practices affected the ability to identify dose-response relationships?
- Is there an animal model in which beryllium induces lung cancer by the same mode of action as in humans?

The committee concludes that a meaningful cancer dose-response assessment cannot be conducted until more information is available on existing or new worker cohorts: complete work history, possible exposure to other carcinogens, and better exposure histories. It may also be necessary to investigate mode of action further with animal studies if a suitable model can be identified. Such studies could help to elucidate the relative importance of peak vs cumulative exposures in cancer incidence.

Furthermore, carcinogenic risk estimates would be of limited utility in light of the committee's recommended approach to preventing beryllium disease. The committee found that it is not possible to reliably identify an exposure magnitude at which there is no risk of sensitization and development of CBD and therefore recommended that the Air Force implement a surveillance and medical-monitoring program to keep exposure as low as feasible to prevent adverse health effects. Recommendations for designing such a program are presented in Chapter 7.

6

Assessment of Other Health End Points

The principal health end points now of interest in connection with inhaled beryllium—beryllium sensitization, chronic beryllium disease (CBD), and lung cancer—were discussed in Chapters 3, 4, and 5. As described in Chapter 3, CBD is primarily a disease of the lungs. Other systemic effects are not common and are usually secondary to CBD or related to extrapulmonary granulomatous lesions. In deriving a reference concentration for beryllium in air based on CBD, the U.S. Environmental Protection Agency (EPA 1998a,b) noted that systemic effects of inhaled beryllium other than those seen in CBD would be expected to occur only after exposure much greater than that after which CBD is observed. The oral reference dose (RfD) derived by EPA (1998a) is based on small-intestine lesions in a long-term study of dogs fed beryllium sulfate. No human studies that could be used to derive an oral RfD were identified by EPA.

This chapter examines the literature relevant to determining whether inhaled beryllium has systemic health effects other than CBD and cancer that might be critical end points for use in deriving health-based standards. The focus is on studies of reproductive and developmental effects because these are often sensitive end points. Studies of oral and parenteral exposure are also considered in some cases. The following specific questions were formulated to guide the literature review:

- Have any studies examined the reproductive or developmental effects of beryllium at doses relevant to current occupational exposures?
- Have any studies distinguished the reproductive or developmental effects of different forms of beryllium?
- Are any other effects of beryllium relevant to current occupational exposures?
- Do effects other than cancer and sensitization that leads to CBD need to be considered in establishing worker health-protection standards?

Those questions are addressed in the following sections. Reproductive and developmental effects of beryllium are considered first, then other potentially relevant health end points.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Reproductive and developmental toxicity of beryllium compounds has been reviewed by EPA (1998b), the Agency for Toxic Substances and Disease Registry (ATSDR 2002), and the American Conference of Governmental Industrial Hygienists (ACGIH 2006). Animal studies have included oral and parenteral exposure but not inhalation exposure. Reproductive and developmental outcomes have not been examined in epidemiologic studies of beryllium workers, and only one study of reproductive and developmental outcomes in workers that included consideration of beryllium exposure was identified.

EPA's (1998b) review focused on hazard assessment of environmentally relevant doses and concluded that "the potential of beryllium to induce developmental and/or reproductive effects has not been adequately assessed" (p. 50). It should be noted that many of the animal studies may have been

conducted at doses that result in maternal toxicity and so might not have assessed effects directly on the fetus independently of effects on the mother.

The animal studies reviewed include a chronic dog-feeding study in which beryllium sulfate was mixed in the diet at three doses (from 0.023 to 1.3 mg/kg per day) and administered to males and females from before mating through weaning of pups (Morgareidge et al. 1976) and two studies previously reviewed by EPA (1991) in which beryllium compounds were administered parenterally to rats (Clary et al. 1975; Mathur et al. 1987). No adverse reproductive or developmental effects were reported in the dog study, and mixed results were reported in the rat studies.

EPA also noted that no reproductive or developmental effects were reported after paternal occupational exposure to beryllium by Savitz et al. (1989), who examined the effect of parents' occupational exposure on risk of stillbirth, preterm delivery, and small-for-gestational-age infants in a case-control study that used data from the 1980 National Natality Survey and the 1980 National Fetal Mortality Survey. For stillbirths, case groups of 2,096 mothers and 3,170 fathers were examined for associations with 18 industrial or chemical categories. No maternal cases were listed for beryllium exposure, but 127 paternal cases associated with beryllium exposure were listed with an adjusted odds ratio (OR) of 1.0 (95% confidence interval [CI], 0.7-1.3). A similar analysis of preterm deliveries (363 mothers and 552 fathers) and small-for-gestational-age infants (218 mothers and 371 fathers) yielded no cases associated with maternal beryllium exposure. For paternal exposure, 23 cases of preterm delivery were associated with beryllium exposure (OR, 1.0; 95% CI, 0.5-2.0), and 16 cases of small-for-gestational-age infants were associated with beryllium exposure (OR, 0.9; 95% CI, 0.5-1.7). Thus, this study suggested no reproductive or developmental effects associated with paternal exposure and could not assess effects of maternal exposures, because of an absence of cases.

ATSDR (2002) did not identify any human studies of reproductive or developmental effects of beryllium. Its review noted that concerns about the adequacy of animal studies of reproductive and developmental effects after oral beryllium exposure were said to be mitigated by the low absorption of ingested beryllium. Inhalation studies were noted as lacking.

Although neither reproductive nor developmental effects were reported in the chronic dog-feeding study (Morgareidge et al. 1976), the design was noted to be nonconventional and to warrant low confidence in interpretation of its findings. The same group also conducted a 2-year study in which beryllium sulfate was administered to rats in drinking water (Morgareidge et al. 1975) and reported no effects in reproductive organs. Neither of those studies is reported in the peer-reviewed literature.

ATSDR (2002) also identified a few parenteral studies that reported developmental effects of beryllium in rats and mice. Mathur et al. (1987) exposed pregnant rats by intravenous injection to beryllium nitrate at one-tenth the dose that was lethal to 50% of the animals (that is, one-tenth the LD_{50}). Normal pups were delivered if the dose was administered on day 1, 12, 13, 15, or 17 after coitus, but all pups died 2-3 days after delivery. If the dose was administered on day 11 after coitus, all fetuses were resorbed. Day 11 is the day before formation of the placenta but a time when the maternal circulation is supplying nutrients to the fetuses. Thus, beryllium exposure early in pregnancy when blastocysts were supported only by uterine secretions did not interfere with implantation, and exposure later in pregnancy after formation of the placenta did not appear to affect in utero development. Developmental effects occurred in pregnant rats after intratracheal injection of beryllium oxide or beryllium chloride (Selivanova and Savinova 1986), and beryllium salts injected into pregnant mice reached the fetus and caused developmental abnormalities in offspring (Bencko et al. 1979; Tsujii and Hashishima 1979).

ACGIH (2006) described five animal studies (Clary et al. 1975; Morgareidge et al. 1975, 1976; Selivanova and Savinova 1986; Sharma et al. 2002) and concluded that "the doses and dose regimes are unlikely to be relevant to human occupational exposure" (p. 4). No human studies were described.

No reproductive or developmental studies of beryllium that were published after the EPA, ATSDR, and ACGIH reviews were identified. Consequently, EPA's conclusion that the potential of beryllium to induce developmental or reproductive effects has not been adequately assessed is still warranted.

OTHER EFFECTS

Extrapulmonary effects of beryllium compounds are not common and are most often secondary to severe lung disease or related to extrapulmonary granulomatous lesions in humans. Systemic effects of beryllium in animals are generally observed only at high doses. ATSDR (2002) provides a comprehensive review of both human and animal data. Cardiovascular effects in humans (cor pulmonale) and animals (heart enlargement or decreased arterial oxygen tension) were judged to be probably secondary to lung disease. Human case studies did not report significant effects on hematologic measures, but intermediate-duration, high-dose exposures caused anemia in several species. Hepatic effects, other than granulomas, have not been reported in humans or animals. Kidney stones and increased blood and urinary calcium have been reported in people with CBD, and a cohort mortality study of beryllium workers found an increased risk of death from chronic and unspecified nephritis, renal failure, and other renal sclerosis (Ward et al. 1992). Renal effects in animals were noted by ATSDR (2002) to be minor at sublethal doses. Some adrenal effects have been reported in animals. Neurologic effects have not been noted in humans or animals after inhalation of beryllium. No literature published after the ATSDR review that would cause increased concern about extrapulmonary effects of beryllium compounds was identified.

SUMMARY

Studies of the extrapulmonary effects of different forms of beryllium have not comprehensively evaluated doses relevant to current occupational exposures, but there is little indication that such studies would yield useful information. Studies of reproductive and development effects and studies of other extrapulmonary effects have generally been conducted only at doses higher than the lowest doses that induce CBD or cancer. The committee concludes that effects other than cancer and sensitization that leads to CBD do not need to be considered in establishing worker health-protection standards. Protection against such health effects will be afforded by exposure guidance designed to prevent CBD or cancer.

7

Designing a Beryllium Exposure- and Disease-Management Program for Workers in the Air Force

Beryllium sensitization (BeS), chronic beryllium disease (CBD), and lung cancer are the principal health concerns related to exposure to beryllium. Because of a lack of quantitative risk information on low exposure and uncertainties associated with factors that contribute to the development of CBD (see Chapter 3), the committee was unable to identify a chronic inhalation exposure level that is unlikely to produce BeS or CBD. Therefore, the committee recommended, in Chapter 3, that an exposure- and disease-management program be implemented to manage potential health risks posed by exposure to beryllium. This chapter provides some general guidelines for designing a preventive program.

EXISTING MEDICAL SCREENING OR SURVEILLANCE PRACTICES

Published beryllium-exposure management programs are summarized in Table 7-1. Deubner and Kent (2007) describe Brush Wellman's extensive beryllium-management program. The goals of the program are to keep beryllium work areas clean; to keep beryllium out of the lungs, off the skin, and off clothing in the work process, in the work area, and on the plant site; and to keep workers prepared to work safely. On the basis of surveillance data, the program reduced BeS from 18% (before program implementation) to 1.1% in 24 months. Cummings et al. (2007) present an analysis of sensitization rates before and after the implementation of Brush Wellman's enhanced beryllium-management program. They also document a BeS reduction associated with the program. The postimplementation sensitization rate was 1%, similar to that in the study by Deubner and Kent. The sensitization rate in preimplementation workers was 8%. Johnson et al. (2001) described a beryllium-management program for atomic-weapons establishments in the United Kingdom. That program is similar to the Brush Wellman program. Its adoption reduced exposures to less than 2 $\mu g/m^3$. The facility has documented only one case of CBD, which was detected by using a medical monitoring program that did not include the beryllium lymphocyte proliferation test (BeLPT). That CBD case is considered unique in that it probably occurred as a result of a systemic reaction to beryllium oxide contamination of a cut. This facility does not routinely evaluate BeS with the BeLPT, so the effect of the program on sensitization and early-stage CBD is unknown.

Several approaches for screening or surveillance of beryllium workers can be found in the scientific literature (see Table 7-2 for some examples). Most of the studies have focused on evaluating the performance of the BeLPT, and were not designed to determine the appropriate selection of tests and the optimal frequency of testing for medical surveillance and screening. As indicated in the table, a questionnaire has been used in most of the studies to include occupational history, occupational exposure, and medical information (such as smoking history, previous respiratory disease, respiratory and dermatologic symptoms, fatigue, weight loss, and medication use). Use of the BeLPT has been included in most surveillance and screening programs since the test has been available; an exception is the UK atomic weapons facility, where the BeLPT was used until the middle 1980s and is now only used on request (Johnson et al. 2001).

TABLE 7-1 Summary of Published Beryllium-Exposure Management Programs

Workers	Program Components	Comments	Reference
Brush Wellman workers	Respiratory protection Dermal protection Work-area and plant hygiene practices Worker training	Program implementation reduced BeS to 1.1% in new workers	Deubner and Kent 2007
Atomic-weapons workers in United Kingdom	Engineering controls Respiratory protection Work-area hygiene practices Medical surveillance for CBD	Program generally keeps exposures below 2 μg/m^3 Only one case of CBD in 400 workers	Johnson et al. 2001
Beryllium workers	*For workers:* Understand risks Avoid inhalation and skin contact Avoid dust-suspending activities Participate in medical surveillance *For employers:* Knowing beryllium content of all materials Substitution of less hazardous materials, if feasible Minimizing number of workers exposed Engineering controls Keeping airborne concentrations as low as possible Exposure monitoring Risk communication Confining beryllium contamination to work area Respiratory protection Dermal protection Medical surveillance		NIOSH 2008
DOE and DOE contractor workers with potential beryllium exposure	Baseline inventory to identify operations and locations of potential beryllium contamination Hazard assessment Initial exposure monitoring Limitation of access to areas containing beryllium Reduction and minimization of exposures through engineering and work-practice controls Keeping exposures below PEL of 2.0 μg/m^3 Provision of respirators when requested by workers Setting of action level at 0.2 μg/m^3 (8-h TWA) Maintaining removable surface contamination below 3 μg/100 cm^2 in designated beryllium-handling areas and below 0.2 μg/100 cm^2 when released to the public or for nonberyllium use For all areas exceeding action level, provision of protective respiratory, clothing, and other equipment; periodic monitoring; regulation of access to that area; installation of hygiene facilities and institution of hygiene practices; posting of warning signs Medical surveillance of all beryllium-associated workers Training of workers who could potentially be exposed Counseling of workers who have diagnosis of BeS or CBD Offer of medical-removal protection to sick or sensitized workers Accurate records of all information gathered Monitoring of the effectiveness of the program and provision of performance feedback		10 CFR 850

TABLE 7-2 Medical Screening Tests Used in Beryllium-Exposed Populations

Workers	Cross-Sectional or Repeated Test Intervals	Tests	Reference
Aluminum smelter	Annual	Qx, spirometry, BeLPT	Taiwo et al. 2008
Beryllium-material production	At hire; 3, 6, 12, 24 mon	BeLPT	Deubner and Kent 2007
Brush Wellman plants	At hire; 3, 6, 12, 24, 48 mon	BeLPT	Donovan et al. 2007
Ceramic	At hire; 3, 6, 12, 24, 48 mon	BeLPT	Cumming et al. 2007
Copper-beryllium alloy distribution	CS	Qx, BeLPT	Stanton et al. 2006
Copper-beryllium alloy	CS	Qx, BeLPT	Schuler et al. 2005
Nuclear facility	CS	Qx, spirometry, CXR, BeLPT	Sackett et al. 2004
DOE nuclear facility	CS	Qx, CXR, BeLPT	Welch et al. 2004
Machining	Every 2 y (new and rehired within 3 mon of starting)	Qx, BeLPT	Newman et al. 2001
UK atomic-weapons facility	Monthly spirometry, annual CXR	Clinical and physical examinations, spirometry, CXR (BeLPT used until middle 1980s, then only if requested)	Johnson et al. 2001
Mining and milling	Quarterly or annual PFT, including DLCO and CXR since 1969, then 1996-1997 Qx and BeLPT	PFT, CXR, later BeLPT, Qx	Deubner et al. 2001a
Ceramic	Annual Qx, PFT, CXR; CS BeLPT in 1992, 1998	Qx, CXR, PFT, BeLPT	Henneberger et al. 2001
Metal alloy and oxide	CS	Qx, BeLPT	Kreiss et al. 1997
Ceramic	CS	Qx, BeLPT, CXR	Kreiss et al. 1996
Nuclear	Two tests at 3-y intervals	Qx, CXR, BeLPT	Stange et al. 1996b
Ceramic	CS	Qx, BeLPT, CXR	Kreiss et al. 1993a
Nuclear	CS	Qx, BeLPT, CXR, spirometry	Kreiss et al. 1993b
Nuclear machining	CS	Qx, BeLPT, CXR, spirometry	Kreiss et al. 1989
Beryllium factory	Every 3 y since 1977	Qx, spirometry, CXR, blood gases	Kriebel et al. 1988
Mine and mill	Twice at 3-y intervals	Spirometry, BeLPT	Rom et al. 1983

ABBREVIATIONS: BeLPT, beryllium lymphocyte proliferation test; CS, cross-sectional; CXR, chest x ray; DLCO, carbon monoxide diffusing capacity; DOE, Department of Energy; PFT, pulmonary-function test; Qx, questionnaire.

CONSIDERATIONS FOR THE AIR FORCE

The committee had little information on current or former workers and the extent or structure of the workforce with potential beryllium exposure, such as enlisted personnel, civilian employees, and subcontractors. The prevalence of BeS or CBD (if any) in Air Force personnel is not known, inasmuch as the service has not performed any systematic surveillance of its workers for BeS or CBD. Thus, the

proposed beryllium exposure- and disease-management program described below is a general outline of a program that should be tailored to the Air Force's needs as more information becomes available.

Figure 7-1 shows a framework for minimizing personnel exposure and risks posed by exposure to aerosolized beryllium in the Air Force. Key aspects of the framework are discussed below, and general recommendations for monitoring and testing are provided. The first years in which the management program is in place will include a period of information-gathering, when more is learned about the type of workplace settings with beryllium exposure in the Air Force and about the prevalence of BeS and CBD, if any, in the settings. With time, the initial testing and monitoring practices should be refined as more information is gathered on the specific risks of BeS and CBD in the Air Force and as any new research findings appear in the scientific literature. In addition, the findings from the management program should be used to consider whether it would be prudent to evaluate beryllium exposures and potential risks to former Air Force workers.

Exposure Assessment

A detailed exposure assessment is a key element of a beryllium-management program. The exposure-assessment strategy should be modeled after the recommendations contained in the American Industrial Hygiene Association's manual for assessing and managing occupational exposures (Ignacio and Bullock 2006). Briefly, the strategy should begin with an initial job or task characterization. The purpose of the initial characterization is to identify all jobs and tasks that have a potential for skin or respiratory beryllium exposure. Beryllium-containing materials should be characterized as to where they are used or were used in the past, their alloy content, their potential for contact that could lead to dermal or inhalation exposure, and the presence of any exposure controls. After the basic characterization, exposures should be assessed with air and surface sampling. As noted in Chapter 2, there are several analytic approaches for detecting airborne beryllium. Air samples are typically measured by either flame atomic absorption spectroscopy or inductively-coupled plasma atomic emission spectrometry, but other methods are available (see Chapter 2). Given the available Air Force sampling data, a method should be chosen that maximizes analytical sensitivity. For jobs or tasks identified as having detectable airborne beryllium, consideration should be given to determining the beryllium particle size distribution by using stationary or personal cascade impactors. Determining the particle size distribution may require pooling samples related to a given job or task to provide detectable quantities of beryllium. Beryllium surface sampling should conform with standard practices (such as the Department of Energy's Chronic Beryllium Disease Prevention Program, 64 Fed. Reg. 68854 [1999]). Samples with surface beryllium exceeding background levels of removable contamination on equipment surfaces should be investigated for the source of contamination. The goal of sampling is to identify jobs that entail detectable airborne or dermal exposure. Workers in those jobs should be targeted for exposure reduction and medical monitoring.

Exposure Reduction and Prevention

Measures should be taken to prevent skin and respiratory exposure to beryllium to the greatest extent possible. The control measures detailed in the National Institute for Occupational Safety and Health (NIOSH 2008) draft document on *Preventing Chronic Beryllium Disease and Beryllium Sensitization* and similar resources from DOE (10 CFR 850) and Brush Wellman (Deubner and Kent 2007). The measures include the following:

- Know the beryllium content of all materials in the workplace. The manufacturers or suppliers of materials containing more than 0.1% beryllium are required to provide this information on material-safety data sheets. Upstream-production information might be needed to assemble a comprehensive list of materials used by the Air Force and its subcontractors.

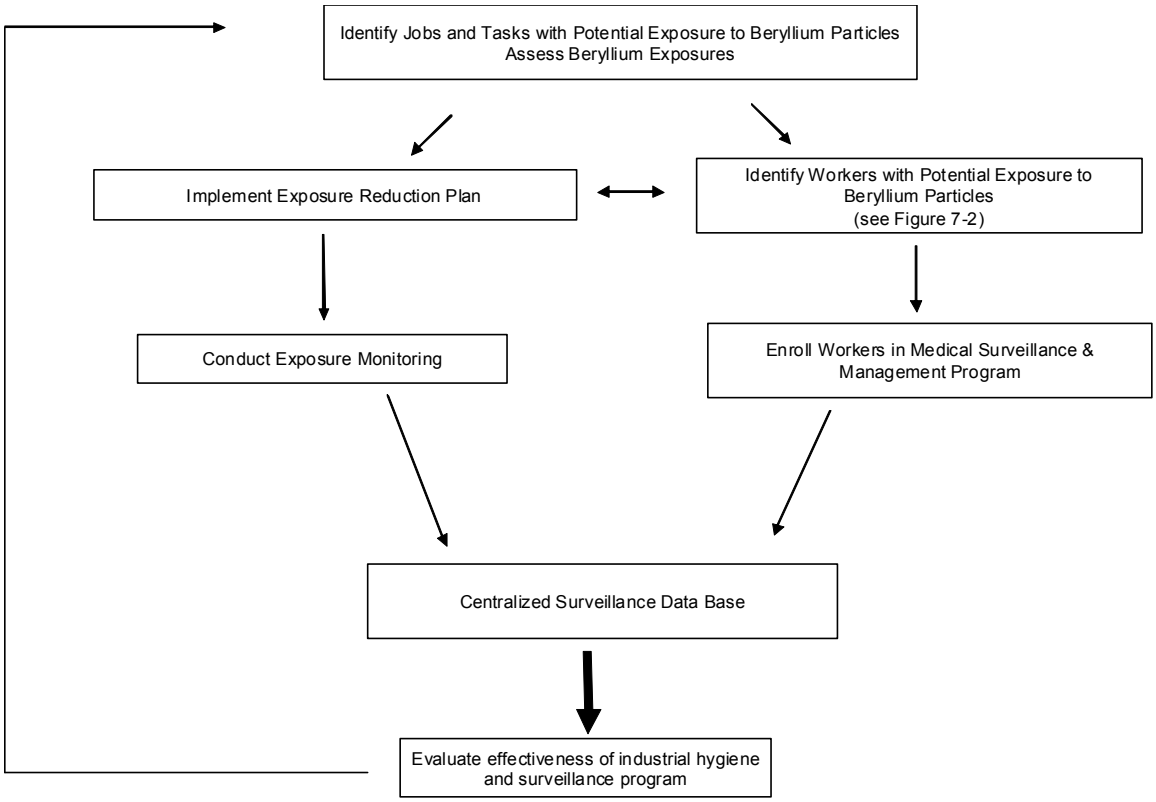

FIGURE 7-1 Beryllium exposure and disease management program.

- Substitute less hazardous materials for those containing beryllium whenever feasible.
- Keep airborne concentrations of beryllium as low as possible because no safe exposure limit for beryllium is known.
- Minimize the number of workers exposed to beryllium dusts, fumes, and contaminated surfaces.
- Install, use, and maintain effective engineering controls for processes that create beryllium dusts and fumes.
- Monitor airborne beryllium concentrations to document the effectiveness of efforts to reduce airborne exposure.
- Inform workers about the risks of BeS, CBD, and lung cancer and the proper procedures for working with beryllium-containing materials.
- Keep beryllium dusts and fumes confined to the immediate work area.
- Avoid the use of cleaning methods that may cause dust to become resuspended in air (for example, dry sweeping, use of compressed air, and other dust-generating methods).
- Prevent beryllium dusts and other contamination from leaving beryllium work areas on equipment or workers' skin, clothing, shoes, and tools.
- Identify and clean areas in and outside the beryllium work zone that may have become contaminated before these recommendations were implemented.
- Establish and maintain an appropriate respiratory-protection program
- Establish and maintain a skin-protection program to protect workers' skin from contamination with beryllium dusts and solutions by keeping work surfaces and work areas clean; providing work gloves, long-sleeved shirts, long pants, and shoes that remain at the workplace; and providing showering and changing facilities.

Worker Education and Training Programs

Worker education and training programs should be in place and should include education of all new and current workers with potential for beryllium exposure as to health risks of beryllium, appropriate exposure reduction, and use of skin and respiratory protective equipment. Such programs have been implemented in a beryllium-products manufacturing plant (Deubner and Kent 2007) and in the Department of Energy's CBD-prevention program (DOE 2001). A similar program should be tailored to the Air Force's work settings and workforce. Such a program could be coordinated with informing workers about the surveillance and medical-management program. The information provided should include the role of various screening and surveillance tests, risks related to the tests, and the health and occupational implications of positive test results. Education and training materials should developed to include information about the medical and employment implications of the results of the BeLPT test and about potential long-term health risks after exposure ends.

Identifying Workers Who Have Beryllium Sensitization or Chronic Beryllium Disease

On the basis of the initial exposure evaluation, Air Force workers with exposure to beryllium—including civilian employees, onsite subcontractors, and workers who may be exposed incidentally—should be evaluated for possible BeS, and those with confirmed BeS should be further evaluated for CBD (see Figure 7-2). The medical screening program, including the BeLPT and diagnosis and management of workers with BeS and CBD, is described in greater detail below. Data from the screening program should be entered into the centralized database to facilitate evaluation of the effectiveness of the program and guide modifications (see discussion below).

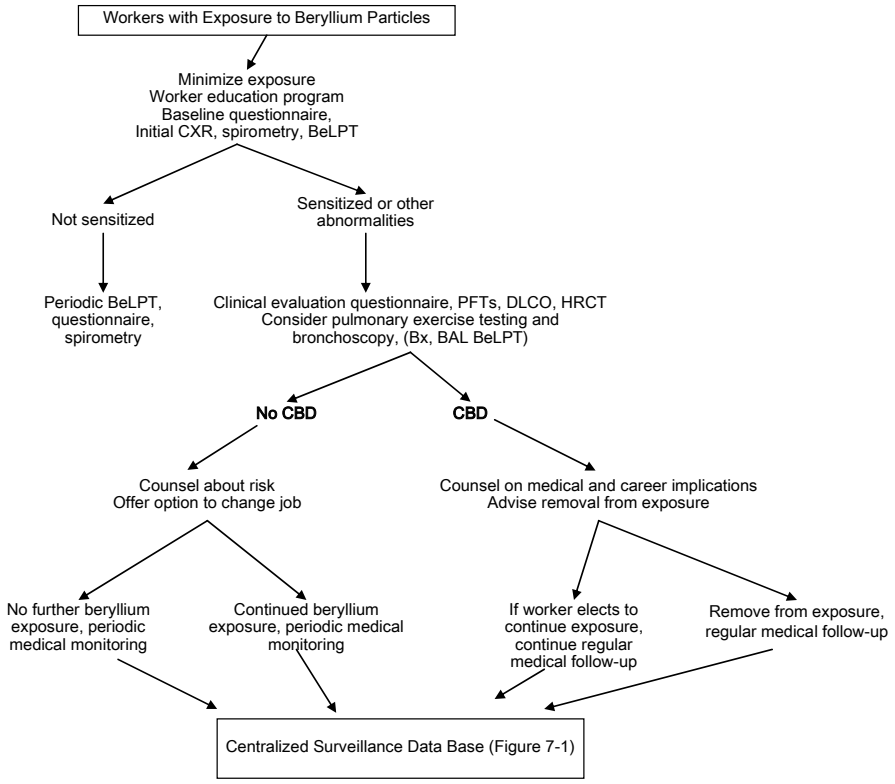

FIGURE 7-2 Medical monitoring approach.

Limiting the Number of Beryllium Workers

Limiting the number of workers exposed to beryllium in the Air Force is consistent with the industrial-hygiene hierarchy of controls. The workers should not only be skilled in operations involving beryllium but be trained in and committed to the safe use of beryllium and control of beryllium exposure as part of the overall beryllium-management plan. Medical screening and surveillance can then be targeted to the workers. Some aspects of this approach have been described in a report of an enhanced preventive model in a large beryllium-products manufacturing plant (Deubner and Kent 2007). The authors described limiting the number of workers exposed to beryllium and reducing worker turnover in areas of beryllium exposure, and they described a wall-enclosed, restricted access zone. They reported that those measures were implemented until engineering control changes could be completed at the plant. They also described enhanced worker preparation through training, education, and motivation.

Centralized Surveillance Database

Data obtained from the beryllium exposure-assessment and worker-surveillance programs at each Air Force site should be entered into a centralized surveillance database (Figure 7-1). Data should include airborne and surface beryllium-sampling data, job and task information, use of personal protective equipment, and clinical information, such as demographics, smoking, job history, results of the BeLPT, spirometry, and additional testing (for example, high-resolution computed tomography and bronchoscopy). The prevalence of BeS and CBD should be determined, and assessments made of possible associations between prevalence and jobs and tasks or exposure. That information should then be used to refine and modify the program. For example, specific sites or job tasks with a higher prevalence of BeS might require greater attention to exposure control or more frequent medical monitoring. The effectiveness of the exposure-reduction plan on quantitative airborne and surface beryllium-sampling data should also be evaluated. In addition to facilitating assessment of the prevalence of BeS and CBD in Air Force workers and the effectiveness of the program, the database could be used as a resource by investigators. The database should include followup clinical data on all workers identified with BeS and CBD so that questions regarding natural history and risk factors for progression can be addressed.

SPECIFICS OF THE MEDICAL SCREENING PROGRAM

Initial Medical Screening

The committee advises that after workers have undergone education and training, including education as to the potential risks and benefits associated with the screening procedures, there be initial screening of all workers with potential for beryllium exposure, including new hires before placement and current employees, and continuing screening of new hires and workers who might be moved from areas of no exposure to areas with potential exposure to beryllium. Each entering and current worker with potential beryllium exposure should receive baseline medical screening that includes a questionnaire, chest radiography, spirometry, and the BeLPT. The questionnaire should include at least demographic information, lifetime workplace exposure history, smoking history, and history of respiratory and dermal disease and symptoms. The BeLPT test should be performed in accordance with the testing algorithm in Appendix B. BeLPT results from initial testing and any necessary retesting should be evaluated and recorded before a worker is allowed to begin work with potential exposure to beryllium.

Outcome of Initial Medical Screening

Initial findings of the questionnaire, chest radiography, and spirometry should be reviewed by an appropriately trained medical provider to determine appropriate job placement and medical followup. Results of the BeLPT test (according to the algorithm in Appendix B) will determine whether the worker is sensitized to beryllium. Those who are not sensitized and have no other findings of concern should be monitored regularly. The frequency of all screening measures cannot be advised with confidence, because no studies have evaluated the optimal interval between screenings. Table 7-2 illustrates the measures that have been used for screening and the intervals used. For examples, the questionnaire has been administered at intervals of 3-12 months, and chest radiography at intervals of 1-3 years at different facilities. Similarly, the frequency of the BeLPT cannot be advised with confidence, because no published studies have addressed it. Some studies have identified development of BeS within 4-8 months of first beryllium exposure in new hires in some work settings, but the clinical importance of detection at 4 months rather than at 1 year has not been determined. In the absence of a clear current estimate of risk in the Air Force, it is suggested that there be initial screening and that the frequency of repeat screening be guided in part by the extent of abnormalities detected. The frequency and extent of monitoring will probably depend on several factors, including information on exposure and the risk of BeS and CBD identified on initial screening. Initially, when there may be some uncertainty as to the risk to the workforce, it would be reasonable to consider annual medical monitoring for those with potential beryllium exposure. The data obtained from exposure assessment and medical monitoring should be collected centrally and reviewed regularly to allow determination of work areas and types of jobs carrying exposure risks and to allow some determination as to the degree of risks of BeS and CBD in exposed workers. Such knowledge should lead to better exposure controls and may allow modification of the program to optimize the frequency of medical monitoring and to determine the relative effectiveness of modes of screening. Others have suggested that the optimal frequency of medical monitoring may be between 1 and 5 years after the initial assessment (Maier 2001; Judd et al. 2003).

BeLPT results that are not reported as normal should be addressed as outlined in Appendix B. An abnormal BeLPT result, unexplained abnormalities seen in chest radiography or spirometry, unexplained respiratory symptoms, or other symptoms should lead to further medical assessment. Potentially, there can be an adverse effect on workers of almost any medical investigation, including emotional stress during a wait for test results. Identification of radiographic abnormalities that may not have true clinical significance can lead to more invasive tests (such as bronchoscopy or open lung biopsy), which have associated risks.

If a worker with evidence of BeS is undergoing further evaluation for possible CBD, investigations would probably include full pulmonary-function tests and high-resolution computed tomography (HRCT) scans of the chest, which pose minimal risk. Bronchoscopy with bronchoalveolar lavage and biopsies poses greater risk and, although generally a sensitive method of diagnosing CBD, may not be appropriate or necessary for all workers with BeS. For example, a worker with an abnormal HRCT scan showing diffuse opacities or pulmonary-function abnormalities might, after evaluation of the risks and benefits related to bronchoscopy, obtain a presumptive diagnosis without undergoing bronchoscopy. A worker with BeS who is asymptomatic and has normal pulmonary-function test results, carbon monoxide diffusing capacity, and HRCT may not want to undergo bronchoscopy, unless abnormalities are found in a regular followup. A worker with BeS or other medical screening results that suggest CBD should be offered removal from beryllium exposure (discussed further below).

Outcome of Further Clinical Evaluation

After the clinical evaluation, there are three possible outcomes:

- *No CBD and no BeS*. These workers will be advised that they can continue their previous jobs and have routine periodic medical screening. Other medical conditions (not related to beryllium) identified in the clinical evaluation should be managed as they would be for non–beryllium-exposed workers.
- *BeS but no CBD*. There is insufficient evidence to determine clearly the effect of continuation of work in an area with potential beryllium exposure for those with BeS. Although BeS is a predictor of CBD, it is not known whether (and by how much) additional beryllium exposure increases the risk of progression to CBD. That uncertainty should be communicated to a sensitized worker, who should be given the opportunity to work in areas without further beryllium exposure with medical removal protection. Workers with BeS who wish to continue to work in an area with potential beryllium exposure should be closely monitored to detect CBD.
- *CBD*. Workers with CBD should discontinue work in areas that have beryllium exposure because of concern about worsening the disease. Although the effect of continuing exposure to beryllium at relatively low concentrations has not been clearly shown, the potential for CBD to become serious suggests that, given the current state of knowledge, it is prudent to avoid further beryllium exposure. Workers with CBD should continue to receive regular medical followup. Workers with CBD who discontinue work with beryllium should receive medical removal protection. If workers understand the risk and elect to continue exposure, their exposure should be kept as low as feasible, and they should have regular medical followup and regular advice about the risk of disease progression.

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Appendix A

Biographic Information on the Committee on Beryllium Alloy Exposures

Charles H. Hobbs *(Chair)* is director of the Toxicology Division of the Lovelace Respiratory Research Institute and vice-president of the Lovelace Biomedical and Environmental Research Institute. He also holds an appointment as clinical professor in the College of Pharmacy of the University of New Mexico. His research interests are in the long-term biologic effects of inhaled materials and the mechanisms by which they occur. His experience covers inhaled nuclear and chemical toxicants and infectious diseases and has ranged from physical and chemical characterization of airborne toxicants to in vitro mechanistic and toxicologic studies of dose-response relationships in laboratory animals. Dr. Hobbs is a national associate of the National Academies and has served on several committees of the National Research Council, including service as chair of the Committee on Animal Models for Testing Interventions Against Aerosolized Bioterrorism Agents and of the Committee on Submarine Escape Action Levels. He received his DVM from Colorado State University.

Patrick N. Breysse is a professor in the Department of Environmental Health Sciences and director of the Division of Environmental Health Engineering of the Johns Hopkins University Bloomberg School of Public Health. He is also program director of the Industrial Hygiene Training Program and director of the Center for Childhood Asthma in the Urban Environment. His main research interest is in exposure assessment, including pollutant-source characterization; exposure measurement and interpretation; development and use of biomarkers of exposure, dose, and effect; and evaluating relationships between sources, exposure, doses, and disease. Dr. Breysse codirected a medical screening program for former Department of Energy workers at the Los Alamos National Laboratory and serves on the laboratory's Beryllium Health and Safety Committee. He is a former chair of the American Conference of Governmental Industrial Hygienists Worldwide. Dr. Breysse received his MHS in occupational safety and health and his PhD in environmental health engineering from the Johns Hopkins University.

Scott W. Burchiel is a professor of pharmacology and toxicology in the College of Pharmacy of the University of New Mexico Health Sciences Center. He is associate dean for research at the college, director of the New Mexico Center for Environmental Health Sciences, and a member of the University of New Mexico Cancer Research and Treatment Center. His research interests are in immunotoxicology, cancer research, pharmacogenomics, and biotechnology. His laboratory examines the effects of drugs and environmental agents on signaling pathways that control lymphocyte activation and apoptosis, proto-oncogene activation, and mechanisms of signaling in human mammary epithelial cells. Dr. Burchiel was a member of the National Research Council Committee on Assessing Human Health Risks of Trichloroethylene. He received his PhD in pharmacology from the University of California, San Francisco.

Lung Chi Chen is an associate professor in the Department of Environmental Medicine of the New York University (NYU) School of Medicine. He is also director of the Inhalation Facility for the National Institute of Environmental Health Sciences Center of Excellence. His research interests are in inhalation toxicology and exposure-response relationships. His recent research has focused on nanoparticle toxicity and functional use, the role of health disparity in air-pollution–induced cardiopulmonary diseases, and gene-environment interactions in environmentally induced diseases. Dr. Chen is vice president-elect of the Inhalation Specialty Section of the Society of Toxicology. He received his MS and PhD in environmental health science from NYU.

David Díaz-Sánchez is chief of the Clinical Research Branch of the U.S. Environmental Protection Agency (EPA). Before joining EPA in 2007, he was an associate professor in the Department of Medicine of the University of California, Los Angeles. His research interests are in the use of human and animal models to understand the ability of environmental agents to affect immune responses, particularly agents that modulate allergic and asthmatic responses. His recent work has focused on how diesel-exhaust particles exacerbate allergy and asthma, the role of phase II enzymes in conferring susceptibility to pollutants, and the role of oxidative stress in susceptibility to particulate matter and in the potency of particles in promoting airway inflammation. Dr. Díaz-Sánchez is a member of the National Ambient Air Monitoring Strategy Subcommittee of EPA's Clean Air Science Advisory Committee. He received his PhD from Guy's Hospital in London.

David G. Hoel is Distinguished University Professor in the Department of Biostatistics, Bioinformatics, and Epidemiology of the Medical University of South Carolina. He also holds an appointment as clinical professor in the Department of Radiology of the University of South Carolina School of Medicine. His research interests are in environmental causes of cancer, risk-assessment models, and epidemiology. Dr. Hoel was elected to the Institute of Medicine in 1988 and was named a national associate of the National Academies in 2001. He received his PhD in statistics from the University of North Carolina at Chapel Hill.

Loren D. Koller is an independent consultant and former professor and dean of the College of Veterinary Medicine of Oregon State University. His expertise is in pathology, toxicology, immunotoxicology, carcinogenesis, and risk assessment. He is a former member of the National Research Council Committee on Toxicology and of several of its subcommittees, including the Subcommittee on Immunotoxicity and the Subcommittee on Zinc Cadmium Sulfide. He serves on the Committee to Review Chemical Agent Secondary Waste Disposal and Regulatory Requirements. He received his DVM from Washington State University and his PhD in pathology from the University of Wisconsin.

David Kriebel is a professor of epidemiology in the Department of Work Environment of the University of Massachusetts Lowell and codirector of the Lowell Center for Sustainable Production. His research interests are in the epidemiology of cancer, nonmalignant respiratory disease, and workplace injury. He has conducted research on human exposure to asbestos, beryllium, formaldehyde, metal-working fluids, and other environmental and occupational substances. Dr. Kriebel also conducts research on epidemiologic methods aimed particularly at improving the use of quantitative exposure data in epidemiology through biologically based dosimetric models. With Harvey Checkoway and Neil Pearce, he is a coauthor of the leading textbook of occupational epidemiology, *Research Methods in Occupational Epidemiology*. He served on two Institute of Medicine committees that evaluated the health effects of exposure to herbicides in Vietnam veterans. He received his ScM in physiology and ScD in epidemiology and occupational health from the Harvard School of Public Health.

Michael J. McCabe, Jr. is an associate professor in the Department of Environmental Medicine of the University of Rochester School of Medicine and Dentistry. He is also director of the Immunomodulators and Immunopathogenesis Program at the university's Environmental Health Sciences Center. His

research interests are in the mechanisms of immunomodulation by metals. The central theme of his research is the cellular and biochemical-molecular mechanisms that control lymphocyte activation and function. His work focuses on lymphocyte signaling pathways as targets for toxic metals that lead to immunosuppression or to autoimmune disease. Dr. McCabe is a past president of the Metals Specialty Section of the Society of Toxicology and was a councilor of the Immunotoxicology Specialty Section. He received his MS and PhD in microbiology and immunology from Albany Medical College.

Carrie A. Redlich is a professor of medicine at the Yale University School of Medicine in pulmonary and critical-care medicine and occupational and environmental medicine and is associate director of the Occupational and Environmental Medicine Program. She is also a staff physician at Yale-New Haven Hospital and West Haven Veterans Administration Hospital. Her research interests are in occupational and environmental lung diseases with a focus on the pathogenesis, diagnosis, and prevention of asthma due to isocyanate exposure. Dr. Redlich was a member of the Institute of Medicine Committee on Gulf War and Health: Review of the Literature on Pesticides and Solvents. She received her MD from the Yale University School of Medicine and her MPH in environmental health from the Yale University School of Public Health.

Rosalind A. Schoof is a consultant in toxicology and risk assessment with Integral Consulting, Inc. She is a board-certified toxicologist with more than 25 years of experience in conducting evaluations of chemical toxicity, health risk assessments for cancer and noncancer end points, and multimedia assessments of exposure to chemicals at diverse mining and mineral-processing sites, manufacturing sites, landfills, incinerators, and other sources of exposure. Dr. Schoof's research interests include the bioavailability of arsenic and metals in soils and dietary exposure to arsenic and metals. She has served on numerous peer-review panels for U.S. agencies and Canadian ministries and has been a member of several National Research Council committees, including the Subcommittee on Toxicological Risks to Deployed Military Personnel. Dr. Schoof received her PhD in toxicology from the University of Cincinnati.

Nancy L. Sprince is a professor in the Department of Occupational and Environmental Health of the University of Iowa and director of the Heartland Center for Occupational Health and Safety, an education and research center funded by the National Institute for Occupational Safety and Health. Her research interests are in the epidemiology of occupational lung disorders in workers exposed to pulmonary toxins and prevention of occupational and agricultural injuries. From 1978 to 1990, Dr. Sprince was director of the Beryllium Case Registry at Massachusetts General Hospital. She served on the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. She received her MD from the Boston University School of Medicine and her MPH in occupational and environmental medicine from the Harvard School of Public Health.

Susan M. Tarlo is a professor in the Department of Medicine and in the Department of Public Health Sciences of the University of Toronto. She is also a respiratory physician at the University Health Network, Toronto Western Hospital, and at the Gage Occupational and Environmental Health Unit of St. Michael’s Hospital in Toronto. Her research interests are in occupational and environmental lung diseases and allergic responses, especially occupational asthma. Dr. Tarlo received her MB BS (MD equivalent) from London University.

Laura S. Welch is medical director of CPWR—The Center for Construction Research and Training, a research institute devoted to improving health and safety in the construction industry. Her research interests are in asbestos-related diseases, other occupational lung diseases, and musculoskeletal disorders. She is also a lecturer in environmental and occupational health at the George Washington University School of Public Health and Health Services. She has held faculty positions at the university’s medical school and at the Yale University School of Medicine. Dr. Welch received her MD from the State

University of New York at Stony Brook and is board-certified in internal medicine and in occupational medicine. She was a member of the Institute of Medicine Committee on Gulf War and Health: Review of the Literature on Pesticides and Solvents.

Appendix B

Air Force Beryllium Program Clinical Decision Logic

This appendix presents the recommended algorithm for using the beryllium lymphocyte proliferation test (BeLPT) in an Air Force beryllium medical-surveillance program, and the rationale for using it (see Figure B-1).

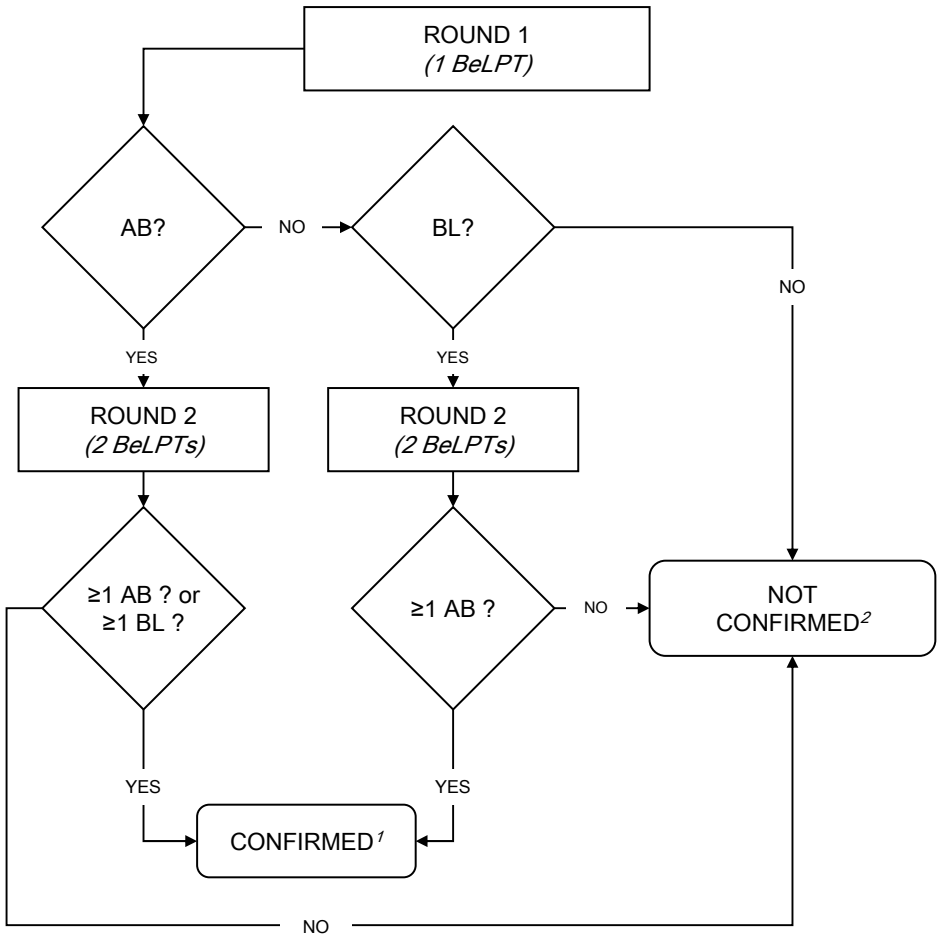

FIGURE B-1 BeLPT algorithm.
[1]Met confirmation criteria of 2AB or 1AB and 1 BL.
[2]Did not meet confirmation criteria.
ABBREVIATIONS: AB, abnormal; BL, borderline.
SOURCE: Middleton et al. 2006. Reprinted with permission; copyright 2006, *American Journal of Industrial Medicine*.

BeLPT Result Definitions

Normal:	All BeLPT test values (stimulation index [SI] or least absolute value [LAV]) within reference range
Abnormal:	Two BeLPT test values (SI or LAV) increased over reference range in a single test
Borderline:	One increased value (SI or LAV) over reference range with at least one control in normal range
Uninterpretable:	Phytohemagglutinin <50 and tetanus toxid <3 with no increase in Sis over reference range
Confirmed abnormal:	Two abnormal BeLPT values or one abnormal and one borderline, either in split sample or in two different samples separated in time

Decision Logic for BeLPT Testing

First Test: Single BeLPT
Second Test: Use a split sample with two laboratories

(1) BeLPT Test 1:

Normal:	NO FURTHER ACTIONS; retest periodically per protocol
Abnormal:	RETEST split sample in two laboratories
Borderline:	RETEST split sample in two laboratories
Uninterpretable:	RETEST split sample in two laboratories

(2) BeLPT Test 1, plus Tests 2 and 3 (any combination of the three):

Two of three tests abnormal:	Clinical evaluation
One abnormal plus one borderline:	Clinical evaluation
One abnormal, other tests normal or uninterpretable	Repeat in 1 year
No abnormal tests (combinations of normal, borderline)	Report as normal, retest per protocol
Uninterpretable, uninterpretable, uninterpretable:	Consult with medical director

(3) Retest periodically per protocol; send sample to single laboratory:

Any confirmed abnormal:	Clinical evaluation
Any single abnormal plus a single borderline:	Clinical evaluation
One abnormal or borderline among all 4 tests:	Periodically retest per protocol

Rationale for Algorithm

Middleton et al. (2006, 2008) reviewed available information on the performance of the BeLPT and calculated the sensitivity and specificity of two testing algorithms (2006). In the "basic" algorithm (outlined in Figure B-1), blood is initially sent to one laboratory, and nonnormal tests are re-evaluated with a split sample sent to two laboratories. The sensitivity of this algorithm is 65.7% (that is, the program would capture 65.7% of true-positive results). The "enhanced" algorithm uses a split sample sent to two laboratories for the initial test; this approach increases the sensitivity to 86%.

As discussed in Chapter 3, the prevalence of beryllium sensitization (BeS) in the population being screened affects the predictive value of the test. As the background prevalence of any condition decreases,

the likelihood that a positive result is a "true" positive decreases, and the likelihood of a false positive increases. Middleton et al. (2008) used the data from Stange et al. (2004) to estimate the positive predictive value (PPV) of a single or confirmed abnormal BeLPT result for sensitization. They calculated that a confirmed abnormal BeLPT result would have a PPV of 0.968 in a population with a 1% prevalence of BeS, and a single abnormal test result would have a PPV of 0.383 in the same population. Middleton et al. estimate a PPV of 0.872 for a single abnormal BeLPT result when the prevalence of BeS is 10%, but in settings with a lower prevalence of BeS a single unconfirmed abnormal has less value because of a low PPV for sensitization.

The committee does not know the prevalence of BeS in the populations of concern for the Air Force. Initial rounds of screening will determine whether the decision to use the basic algorithm is appropriate. If the prevalence of BeS in the population is higher than 5%, the committee recommends that the Air Force use the enhanced algorithm because of its increased sensitivity.

The committee recommends that the Air Force explore the feasibility of establishing a harmonization protocol between two laboratories (see Chapter 3). If the harmonization program is successful and the split tests converge to a high level of agreement with each other, the Air Force should consider the use of a single sample for the second confirmatory test rather than a split sample.

Most medical-surveillance programs for beryllium use all available tests to determine whether a person has a confirmed abnormal test result. For example, if a person has a single abnormal test result among three samples in the initial round of screening and then has a single abnormal sample when tested in any later year, the person would be considered to have a confirmed abnormal. This approach is more sensitive than one that would require confirmation of a single abnormal result in the same round of testing. The committee does not have enough information on the performance of the BeLPT to recommend how to interpret BeLPT results over the timeframe of several years. The committee therefore recommends that the Air Force use the approach that is generally accepted and use all available tests to determine whether a person has a confirmed abnormal test result. If the Air Force is able to achieve harmonization between two laboratories, the variation in a single person's test results is likely to decrease.

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Preface

Beryllium is a lightweight metal that is used for its exceptional strength and high heat-absorbing capability. Beryllium and its alloys can be found in many important technologies in the defense and aeronautics industries, such as nuclear devices, satellite systems, radar systems, and aircraft bushings and bearings.

Pulmonary disease associated with exposure to beryllium has been recognized and studied since the early 1940s, and an occupational guideline for limiting exposure to beryllium has been in place since 1949. Over the last few decades, much has been learned about chronic beryllium disease and factors that contribute to its occurrence in exposed people. Despite reduced workplace exposure, chronic beryllium disease continues to occur. In addition, beryllium has been classified as a likely human carcinogen by several agencies, such as the International Agency for Research on Cancer, the National Toxicology Program, and the U.S. Environmental Protection Agency. Those developments have led to debates about the adequacy of the long-standing occupational exposure limit for protecting worker health. To help to determine the steps necessary to protect its workforce from the effects of beryllium used in military aerospace applications, the U.S. Air Force asked the Committee on Toxicology of the National Research Council to conduct an independent review of the scientific literature on beryllium and to estimate chronic inhalation exposure levels that are unlikely to produce adverse health effects in military personnel and civilian contractors.

In response to the Air Force's request, the National Research Council convened the Committee on Beryllium Alloy Exposures, which prepared this report. The members of the committee were selected for their expertise in pulmonary and occupational medicine, epidemiology, industrial hygiene, inhalation toxicology, immunotoxicology, pathology, biostatistics, and risk assessment (see Appendix A for biographic information on the members).

To help the committee in its review, two data-gathering meetings were held in early 2007. The committee is grateful to the people who gave presentations on their research in and experience with beryllium exposure and disease. They include John Balmes (University of California, San Francisco), David DeCamp (Air Force Institute of Operational Health), Terry Gordon (New York University School of Medicine), Kathleen Kreiss (National Institute for Occupational Safety and Health), David Louis (Air Force Materiel Command), Lisa Maier (National Jewish Medical and Research Center), Aleksandr Stefaniak (National Institute for Occupational Safety and Health), and Paul Wambach (U.S. Department of Energy).

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of the independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following for their review of this report: John Balmes, University of California at San Francisco; Marc Kolanz, Brush Wellman, Inc.; Kathleen Kreiss, National Institute for Occupational Safety and Health; Michael Luster, consultant; Lisa Maier, National Jewish Medical and Research Center; David Michaels, the George Washington University; Martha Sandy, California Environmental Protection Agency; and Timothy Takaro, Simon Fraser University.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by Frank Speizer, Harvard School of Public Health. Appointed by the National Research Council, he was responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the authoring committee and the institution.

The committee is grateful for the assistance of National Research Council staff in preparing the report. It particularly wishes to acknowledge the support of Project Director Susan Martel, who coordinated the project and contributed to the committee's report. Other staff members who contributed to this effort are James Reisa, director of the Board on Environmental Studies and Toxicology; Patrick Baur, research assistant; Tamara Dawson, program associate; Norman Grossblatt, senior editor; and Mirsada Karalic-Loncarevic, manager of the Technical Information Center.

Finally, I thank all the members of the committee for their efforts throughout the development of this report.

Charles H. Hobbs, DVM
Chair, Committee on Beryllium Alloy Exposures

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AEC	Atomic Energy Commission
ATSDR	Agency for Toxic Substances and Disease Registry
BAL	bronchoalveolar lavage
BeLPT	beryllium lymphocyte proliferation test
BeS	beryllium sensitization
CBD	chronic beryllium disease
CI	confidence interval
COT	Committee on Toxicology
DLCO	carbon monoxide diffusing capacity
DLCO/VA	carbon monoxide diffusing capacity per liter of alveolar volume
DOE	U.S. Department of Energy
EPA	U.S. Environmental Protection Agency
HLA	human leukocyte antigen
HRCT	high-resolution computed tomography
IARC	International Agency for Research on Cancer
LANL	Los Alamos National Laboratory
LOAEL	lowest-observed-adverse-effect level
MHC	major histocompatibility complex
MIF	migration-inhibitory factor
MMAD	mass median aerodynamic diameter
MOUDI	micro-orifice uniform deposition impactor
NIOSH	National Institute for Occupational Safety and Health
NTP	National Toxicology Program
OEL	occupational exposure limit
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PPE	personal protective equipment
PPV	positive predictive value
RfD	reference dose
SMR	standardized mortality ratio
SSA	specific surface area
SUF	serum ultrafiltrate
TGF	transforming growth factor
TLV	Threshold Limit Value
TRI	Toxic Release Inventory
TWA	time-weighted average
VD/VT	ratio of dead space to tidal volume