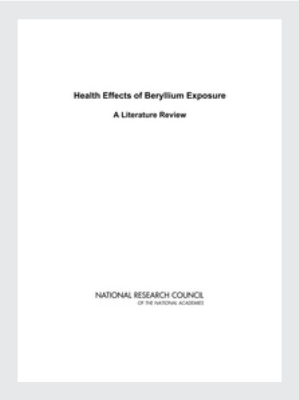

Health Effects of Beryllium Exposure: A Literature Review

DETAILS

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Health Effects of Beryllium Exposure

A Literature Review

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 light-weight metal that is used for its exceptional strength and high heat-absorbing capability. Beryllium and its alloys can be found in many important technologies of the defense and aeronautics industries, including electro-optical targeting and infrared countermeasure devices, missile systems, radar systems, nuclear devices, satellite systems, rocket propellants, and navigational systems.

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. In addition, beryllium has been classified as a likely human carcinogen by several agencies (e.g., 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 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 agency'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 for biographic information on the members).

The committee was asked to produce two reports. The first is to provide a review of the scientific literature on beryllium, and the second will expand more critically on that review in considering the maximum chronic inhalation exposure levels that are unlikely to produce adverse health effects, estimating carcinogenic risks, and developing guidance on testing methods for surveillance and monitoring of worker populations. In this, its first report, the committee identifies the scientific literature that will help to form the basis of its recommendations in the second report. The review focuses on the most important health risks: beryllium sensitization, chronic beryllium disease, and cancer.

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, of the University of California, San Francisco; David DeCamp, of the Air Force Institute of Operational Health; Terry Gordon, of the New York University School of Medicine; Kathleen Kreiss, of the National Institute for Occupational Safety and Health; David Louis, of the Air Force Materiel Command; Lisa Maier, of the National Jewish Medical and Research Center; Aleksandr Stefaniak, of the National Institute for Occupational Safety and Health; and Paul Wambach, of the 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: Scott Bartell, University of California at Irvine; David Deubner, Brush Wellman, Inc.; Meryl Karol, University of Pittsburgh; Kathleen Kreiss, National Institute for Occupational Safety and Health; Joseph Landolph, Jr., University of Southern California; and Lisa Maier, National Jewish Medical and Research Center.

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 this report was overseen by Frank Speizer, Harvard Medical School. Appointed by the National Research Council, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author 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; Tamara Dawson, senior program assistant; Norman Grossblat, 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

Contents

Contents

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 histocompatability complex
MIF	migration inhibitory factor
MMAD	mass median aerodynamic diameter
MOUDI	micro-orifice uniform deposition impactor
NIOSH	National Institutes of Occupational Safety and Health
NRC	National Research Council
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

Health Effects of Beryllium Exposure

A Literature Review

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 exposed to high concentrations of beryllium have been reported to have acute beryllium disease, a pneumonitis-like lung condition, often reversible upon removal from exposure and supportive respiratory care. There was a decrease in incidence of acute beryllium disease in the 1940s when respiratory exposure to beryllium became better controlled in the workplace. Beryllium can also induce a condition known as chronic beryllium disease (CBD), a systemic granulatomous 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's Committee on Toxicology (COT) conduct an independent evaluation of the scientific literature on beryllium, provide risk estimates for cancer and noncancer health end points, and make recommendations about specific tests for surveillance and biomonitoring of workers. The request specified that two reports be produced to accomplish those tasks (see Box S-1). The first is to provide a review of the scientific literature on beryllium, and the second will expand more critically on the review in considering the maximum chronic inhalation exposure levels that are unlikely to produce adverse health effects, in estimating carcinogenic risks, and in providing guidance on testing methods for surveillance and monitoring of worker populations and other specific issues detailed in the statement of task. In response to the U.S. Air Force request, COT convened the Committee on Beryllium Alloy Exposures, which prepared this first report. The report identifies the available toxicologic, epidemiologic, and other literature on beryllium that is most relevant for addressing the statement of task, focusing primarily on beryllium sensitization, CBD, and cancer.

BOX S-1 Statement of Task for 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.

SENSITIZATION AND CHRONIC BERYLLIUM DISEASE

Clinical and Epidemiologic Studies

It is well established that beryllium can cause sensitization and CBD. Sensitization is an immune response, not a disease, and does not have any symptoms. It is usually detected with the beryllium lymphocyte proliferation test (BeLPT), an in vitro test that measures lymphocyte proliferation in peripheral blood cells or bronchoalveolar lavage (BAL) cells. CBD is a systemic granulomatous disorder that affects mainly the lungs. It can present with a variety of other effects that may include respiratory symptoms, radiographic abnormalities, and deficits in lung function. Since its pathogenesis involves a beryllium-specific, cell-mediated immune response, CBD cannot occur without sensitization.

Epidemiologic studies performed on cohorts of workers exposed to various forms of beryllium in different industries have indicated that sensitization and CBD can occur after exposure to beryllium even at concentrations below the current occupational exposure limit of 2 $\mu g/m^3$. The studies have also shown that the incidence of CBD in workers depends on the industry or process, as well as the job category, and that sensitization does not always progress to CBD. There is growing evidence that skin exposure can contribute to sensitization and development of CBD.

Progression to CBD appears to be influenced not only by the magnitude of beryllium exposure but also by the physiochemical properties of the form of beryllium (such as composition and particle size), the genotype and phenotype of the exposed person, and probably the route of exposure. Other possible risk factors that have not been systematically addressed include smoking status, race, sex, concurrent exposures, and other environmental stressors. There is little published information on the rate of progression from asymptomatic immunologic sensitization to CBD.

Beryllium Lymphocyte Proliferation Test

In the BeLPT, a test for sensitization to beryllium, mononuclear cells derived from peripheral blood or 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 CBD and for medical surveillance of workers. For example, a positive BeLPT result differentiates

between CBD and other lung diseases, such as sarcoidosis and chronic obstructive pulmonary disease. When the test is used on a population basis, rather than as a screening or diagnostic test, it is reportedly more useful than traditional air sampling in identifying facilities and areas in a given facility that have substantial beryllium exposure. Screening of healthy exposed workers with the BeLPT has also enabled the detection of beryllium sensitization in asymptomatic workers and earlier diagnosis of CBD.

In its second report, the committee will discuss aspects of the use of the BeLPT in routine surveillance and medical monitoring, including the value of the BeLPT in predicting CBD, protocols for further followup tests after a positive BeLPT result, the likelihood of developing CBD after a true positive test, and a standardized method for achieving consistent test results in different laboratories.

Animal Models

Several animal models of CBD have been studied, including models in mice, dogs, and monkeys. Some immunologic and pulmonary effects similar to those in CBD have been induced in the animal models, but the nature and course of the disease were not exactly the same as in human CBD. For example, the beryllium-induced disease in animals appears to regress when exposure is stopped, whereas in humans it progresses. In general, the exposure that was required to produce the disease in animals was greater by several orders of magnitude than the exposure that has been implicated in human CBD. In addition, it is now clear from animal and human data that susceptibility to CBD has a genetic component. Efforts are under way to create humanized mouse models that might be useful in clarifying the interactions of beryllium with specific target molecules in tissues that may lead to sensitization and progression to CBD in humans.

Influence of Physiochemical Properties

Metal processing operations produce beryllium particles that can be inhaled or deposited on the skin. Differences in the number, composition, structure, size, and surface area of the particles affect their deposition in the lung and their bioavailability. In general, the respirable fraction of beryllium aerosols (particles less than 10 μm in diameter) is a better indicator of exposure than is total mass. However, recent research indicates that surface area and dissolution rate in the lungs also contribute to the rate of release of beryllium ions. How all the relevant factors are combined to achieve a rate of release sufficient to activate T lymphocytes and to initiate and sustain a granulomatous response remains to be elucidated.

Genetic Susceptibility

As noted above, only a fraction of people who are exposed to beryllium become sensitized, and only some of those who are sensitized develop CBD. Attempts to identify the genetic components involved in susceptibility have centered mainly on investigating polymorphisms of the major histocompatibility complex (MHC) class II and proinflammatory genes. Research has indicated that an allele of the HLA-DP gene containing glutamic acid at the 69th position of the β chain (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.

It is clear from the committee's review that the data on beryllium sensitization and CBD will be critical in its consideration of acceptable chronic inhalation exposure levels. The key datasets and uncertainties associated with exposure estimates, genetic susceptibility, and forms of beryllium exposure will be detailed in the committee's second report.

CANCER AND OTHER EFFECTS

There is evidence from many controlled studies that exposure to beryllium can cause lung cancer in rats. 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 the International Agency for Research on Cancer, the U.S. Environmental Protection Agency, and the National Toxicology Program. After the cancer classifications were formed, critiques and alternative analyses of the epidemiologic investigations took place. In its second report, the committee will consider the collective evidence in determining whether any of the available studies are appropriate for establishing carcinogenic risk estimates.

In studies of health end points other than CBD and cancer, adverse effects have generally been observed only at doses higher than the lowest doses that induce CBD or cancer.

1

Introduction

Beryllium is a low-density metal that is used in a number of industries, including the automotive, aerospace, defense, medical, and electronics industries, for various applications 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 brakes, 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, gyroscopes, military-vehicle armor, 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 of 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 (NIOSH), 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-

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

Agency	Year	Guideline or Action	Notes and References
DOE	1949	2 $\mu g/m^3$ OEL (DWA)	DWA is averaged from samples over quarterly periods
	1999	0.2 $\mu g/m^3$ (8-h TWA action level)	Action level triggers worker-protection measures; issued while waiting for OSHA to complete rule-making (64 Fed. Reg. 68854 [1999]).
	2006	Worker safety and health program	71 Fed. Reg. 6858 (2006)
ACGIH	1959	2 $\mu g/m^3$ TLV (8-h TWA)	ACGIH 2006
	1975	A2 carcinogen (suspected human carcinogen)	ACGIH 2006
	1997	A1 carcinogen (confirmed human carcinogen)	ACGIH 2006
	1999	0.2 $\mu g/m^3$ TLV (8-h TWA, inhalable particulate mass, sensitizer; *notice to change*)	ACGIH 2006
	2005	0.05 $\mu g/m^3$ TLV (8-h TWA, inhalable particulate mass, sensitizer, skin exposure; *notice of intended change*)	ACGIH 2006
NIOSH	1972	2 $\mu g/m^3$ REL (8-h TWA)	NIOSH 1972
	1977	0.5 $\mu g/m^3$ REL (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	2 $\mu g/m^3$ PEL (8-h TWA)	PEL was adopted from ANSI standard (OSHA 2002)
	1975	1 $\mu g/m^3$ PEL (8-h TWA; *proposed value*)	Proposed value is based on presumption of carcinogenicity; never promulgated (40 Fed. Reg. 48814 [1975]; OSHA 2002)
	1999, 2001	OSHA petitioned to issue an emergency temporary standard	Petition denied by OSHA, but OSHA stated its intent to begin data-gathering (OSHA 2002)
	2002	Request for information issued	67 Fed. Reg. 70700 (2002)
AIHA	1964	2 $\mu g/m^3$ hygienic standard (8-h TWA)	AIHA 1964
ANSI	1970	2 $\mu g/m^3$ OEL for particles $\leq$5 μm (8-h TWA)	ANSI 1970
IARC	1993	Human carcinogen (Group 1)	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)
		Community PEL (24-h ambient air limit) = 0.01 $\mu g/m^3$	40 CFR § 61.32

ABBREVIATIONS: ACGIH, Agency for Toxic Substances and Disease Registry; AIHA, American Industrial Hygiene Association; ANSI, American National Standards Institute; 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.

atom basis. Mercury and lead had occupational exposure limits of around 100 μg/m^3, so 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 μg/m^3 was evaluated periodically in the 1960s; each time, it was deemed adequate because acute beryllium disease has become a rare occurrence and the incidence of CBD was considerably reduced, even though the standard was not routinely achieved at facilities (Kolanz 2001).

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 a role 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 μg/m^3 on the presumption that beryllium was a carcinogen. However, that revision was never promulgated, because of a Supreme Court ruling that existing OSHA standards can be made more stringent only if there is documented evidence that there is significant risk in the workplace (Industrial Union Dept. AFL-CIO vs American Petroleum Institute, 448 US 607 [1980]). 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. In 2002, the agency issued a formal request for information (67 Fed. Reg. 70700 [2002]), but it has not yet issued any updates.

Other agencies have taken action in re-evaluating their occupational exposure guidelines for beryllium. In 1999, DOE established an action level of 0.2 μg/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 μg/m^3 to be inadequate to protect worker health. In 2005, ACGIH proposed to lower its Threshold Limit Value (TLV) for beryllium to 0.05 μg/m^3 (ACGIH 2006). That lower value is intended to prevent sensitization and CBD.

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 and progression to CBD. Observations from 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 μg/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 other 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 μg/m^3.

EPA also 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 μg/m^3. For beryllium, the unit risk is estimated to be 2.4×10^{-3} per μg/m^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). Dose-response assessments from animal studies yielded similar estimates of risk, but EPA considered epidemiologic data to be a better basis for quantifying 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 in the process of being published appeared to have exposure data that might be suitable for performing quantitative cancer estimates. Until those data were published, EPA recommended that its original unit risk of 2.4×10^{-3} per $\mu g/m^3$ be retained. On the basis of that value, it was 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. 2001a), but EPA has issued no new reassessment of beryllium cancer risks.

COMMITTEE'S TASK

An ad hoc committee under the oversight of the standing Committee on Toxicology (COT) of the National Research Council was tasked with writing two reports in support of the development of chronic inhalation exposure levels for beryllium used in military aerospace applications. For this, its first report, the committee was asked to provide an independent review of the toxicologic, epidemiologic, and other relevant data on beryllium. It was asked to review both carcinogenic and noncarcinogenic effects.

In its second report, which is in development, 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 (such as thin-slice computed-tomography, bronchoscopy and biopsy), the likelihood of developing CBD after a true positive test, and a standardized method to achieve 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.

COMMITTEE'S APPROACH

To accomplish its first task, the committee held two meetings in February and April 2007. The meetings involved data-gathering sessions that were open to the public. The committee heard presentations from the U.S. Air Force and from researchers in the 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. This report provides a survey of the literature on beryllium that was available by the end of April 2007. The purpose is to identify areas on which to focus a more critical review. In the second report, the committee will expand upon the first report by providing a more critical analysis of the literature (including any new publications), establishing exposure-based health-protection standards, and evaluating tests for screening and surveillance of workers.

ORGANIZATION OF THE REPORT

The remainder of this report is organized in four 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 scientific literature on beryllium sensitization and CBD, including what is known about pathogenesis, mode of action, and genetic susceptibility. Chapter 4 focuses on the evidence of beryllium's carcinogenic potential. Other health end points, such as reproductive and developmental effects, are reviewed in Chapter 5.

2

Exposure Assessment

The literature describing exposure to beryllium has been reviewed to provide the basis for examining questions relevant to identifying exposure-response relationships and the development of health-protection standards. Although worker-protection standards are the focus of this effort, an understanding of natural background exposures and anthropogenic exposures in other settings provides a useful context for understanding occupational exposures that lead to disease. Consequently, these exposures are briefly discussed here. This literature review has been conducted with the recognition that appropriate standards may vary with health end point. Exposures that lead to the principal end points of concern in connection with beryllium now—cancer and chronic beryllium disease (CBD)—are likely to have distinct physiochemical and dose-response characteristics.

The following specific questions were formulated to guide the 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 exposures to beryllium, and how have changes in workplace practices changed beryllium exposures?
- How 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 exposures? 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 exposures to beryllium are described next, and later sections examine sampling and analytic methods and exposure metrics for air and surface contamination and skin exposures.

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 with 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 stronger 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 $(CH_3)_2Be$ (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 range from less than 1 to 15 mg/kg (ATSDR 2002). In its review of beryllium, ATSDR (2002) reported that surveys have 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 water concentrations 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 less than the detection limit of 0.03 ng/m^3 (ATSDR 2002). Natural sources of airborne beryllium are windblown dust and volcanic particles, estimated to contribute 5 and 0.2 metric tons per year, respectively, to the atmosphere (Table 2-1). The principal anthropogenic contribution from airborne emissions 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, 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 2-3 orders of magnitude greater than ambient air concentrations.

As of 1991, Rossman et al. (1991) reported that 45 beryllium-containing minerals had been identified, including silicates, aluminum silicates, and aluminum oxides. Four of them were commercially important: beryl, phenakite, bertrandite, and chrysoberyl. Unlike such metals as lead and

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 (TRI) are maximum amounts released by each industry.
[d]The 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.

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 was substantially increased 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 that time, 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 to air, water, underground injection, and land are summarized in Table 2-2 for beryllium and Table 2-3 for beryllium compounds. Releases of beryllium are exceptionally high in Ohio because the sole U.S. producer and processor of beryllium (Brush Wellman) is located there. Releases of beryllium compounds are more dispersed around the country because there are many more companies and industries that 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 about a dozen industries (see Table 2-4). As described by Kreiss et al. (2007), its diverse uses may put a growing number of workers at risk of beryllium exposure. Henneberger et al. (2004) relied on sampling compliance data from the Occupational Safety and Health Administration (OSHA) to estimate that 134,000 U.S. workers are potentially exposed to beryllium; however, Kreiss et al. (2007) believe that the number is far higher because OSHA has not sampled for beryllium in military and nuclear-weapons cycle workplaces. Other workplaces, such as those recycling electronic equipment, may also be a source of previously unsuspected exposure.

TABLE 2-2 Releases of Beryllium Metal to the Environment from Facilities that Produce, Process, or Use It (TRI99 2002)

		Reported Amounts Released (lb/year)[a]						
State[b]	Number of Facilities	Air[c]	Water	Underground Injection	Land	Total On-Site Release[d]	Total Off-Site Release[e]	Total On- 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 (TRI) are maximum amounts released by each facility.
[b]Postal Service state abbreviations are used.
[c]The sum of fugitive and stack releases is included in releases to air from a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off site, including to publicly owned treatment works (POTWs).
SOURCE: ATSDR 2002.

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

		Reported Amounts Released (lb/year)[a]						
State[b]	Number of Facilities	Air[c]	Water	Underground Injection	Land	Total On-Site Release[d]	Total Off-Site Release[e]	Total On- 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 (TRI) are maximum amounts released by each facility.
[b]Postal Service state abbreviations are used.
[c]The sum of fugitive and stack releases is included in releases to air from a given facility.
[d]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[e]Total amount of chemical transferred off site, including to publicly owned treatment works (POTWs).
SOURCE: ATSDR 2002.

TOXICOKINETICS

The toxicokinetic profile of beryllium compounds varies with solubility; more soluble forms undergo greater systemic absorption, distribution, and urinary elimination. EPA (1998b) did not identify any human studies of the deposition or absorption of inhaled beryllium but provides a review of the available animal studies. A more detailed review is provided by the Agency for Toxic Substances and Disease Registry (ATSDR 2002). The more soluble compounds were 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 via alveolar macrophages. The clearance of insoluble compounds from the lung was generally shown to be biphasic, with clearance half-times of days (via mucus transport and alveolar macrophages) to years (by dissolution and other translocation mechanisms) (Schlesinger 1995; NCRP 1997). In humans, residence times in the lung were assumed to

TABLE 2-4 Industries That Use Beryllium

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

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be years because of the presence of insoluble beryllium many years after cessation of occupational exposure (ATSDR 2002).

Substantial fractions of inhaled beryllium doses are removed by mucociliary clearance and enter the gastrointestinal tract. Gastrointestinal absorption is less than 1%, so most beryllium taken in orally and much taken in by inhalation (that is cleared and subsequently ingested) is excreted in feces (EPA 1998b). Beryllium that is cleared from the lung and absorbed into the systemic circulation is distributed primarily to the skeleton, liver, and tracheobronchial lymph nodes. ATSDR (2002) and EPA (1998b) suggest that skin absorption of beryllium compounds in the systemic circulation is minimal, although absorption through bruises and cut wounds has been demonstrated (Rossman et al. 1991). Nevertheless, after skin contact beryllium may become bound to epidermal constituents, such as alkaline phosphatase and nucleic acids, as has been demonstrated in guinea pig epidermis (Belman 1969).

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 localized areas with greater concentrations would be expected around coal-fired power plants and other facilities that emit beryllium. Cigarette smoke contains various low amounts of beryllium but is not known to be a significant source of inhaled

beryllium (ATSDR 2002). During the early 1970s, increased aerosolized beryllium from newly ignited camp-lantern mantles was reported. The mantles were reported to contain 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 µg/L 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.

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 are available dating back to the 1930s and 1940s.

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-µg/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 µg/m^3. Stefaniak et al. (2003a) reported on exposure at Los Alamos National Laboratory (LANL) dating back to the 1940s that averaged 32 µg/m^3. Exposures to beryllium have generally decreased over time. In 1930-1950, exposures 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 to tenths of a microgram per cubic meter. While this indicates a general trend, it should be noted that beryllium exposures can vary considerably and there was potential for exposures outside those general ranges.
- Beryllium exposure within a given facility is highly variable. Stefaniak et al. (2003a) indicate annual geometric standard deviations (GSDs) ranging from 2 to 14 for exposures within LANL. Barnard et al. (1996) reported a coefficient of variation of 120% in personal exposure at Rocky Flats. Day et al. (2007) report a GSD of 3.4 for area air samples collected within a copper-beryllium alloy facility.
- Within beryllium production facilities, hot process environments (such as foundry and furnace operations) generally have the highest exposure (Kriebel et al. 1988; Johnson et al. 2001; Sanderson et al. 2001a). In contrast, Cullen et al. (1987) report the highest exposure at a precious-metal refinery for ball-mill and crusher job titles.
- Hydrolysis and wet grinding operations produced the highest exposure within 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). Kreiss et al. (1996) report machining and lapping as high-exposure jobs at a beryllium ceramics plant.
- Maintenance workers are at risk for high uncontrolled exposure (Donaldson and Stringer 1980; Stange et al. 1996b).
- Area samples underestimate exposure and are not statistically correlated with personal exposure (Donaldson and Stringer 1980; Barnard et al. 1996; Stange et al. 1996a; Johnson et al. 2001).

TABLE 2-5 Summary of Beryllium Airborne-Exposure Studies

Reference	Setting	Sample Type	Summary of Key Findings	Comments
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 Geometric mean: 0.21 μg/m^3 2% of samples were >2 μg/m^3 55% of samples were >0.2 μg/m^3 *2000-2003* Range: <0.02-53.3 μg/m^3 Median: 0.18 μg/m^3 Geometric mean: 0.18 μg/m^3 4% of samples were >2 μg/m^3 50% of samples were >0.2 μg/m^3 Production support *1994-1999* Range: <0.02-0.80 μg/m^3 Median: 0.10 μg/m^3 Geometric mean: 0.11 μg/m^3 <1% of samples were >2 μg/m^3 29% of samples were >0.2 μg/m^3 *2000-2003* Range: <0.02-7.70 μg/m^3 Median: 0.04 μg/m^3 Geometric mean: 0.04 μg/m^3 <1% of samples were >2 μg/m^3 12% of samples were >0.2 μg/m^3 Administration *1994-1999* Range: <0.20 μg/m^3 *2000-2003* Range: <0.02-0.35 μg/m^3 Median: 0.02 μg/m^3 Geometric mean: 0.02 μg/m^3 <1% of samples were >2 μg/m^3 <1% of samples were >0.2 μg/m^3	
Day et al. 2007	Alloy strip and wire finishing	Area	0.003 μg/m^3 (GM), 3.4 (GSD) 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 Geometric mean: 0.04 µg/m^3 <1% of samples were >2 µg/m^3 9% of samples were >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 Geometric mean: 0.03 µg/m^3 <1% of samples were >2 µg/m^3 2% of samples were >0.2 µg/m^3 <u>Production support</u> Range: <0.02-0.13 µg/m^3 Median: 0.01 µg/m^3 Geometric mean: 0.02 µg/m^3 <1% of samples were >2 µg/m^3 <1% of samples were >0.2 µg/m^3 <u>Administration</u> Range: <0.02-0.32 µg/m^3 Median: 0.01 µg/m^3 Geometric mean: 0.02 µg/m^3 <1% of samples were >2 µg/m^3 2% of samples were >0.2 µg/m^3	
Rosenman et al. 2005	Processing facility in 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 were presented in relation to subjects classified with BeS or CBD or as normal

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TABLE 2-5 *Continued*

Reference	Setting	Sample Type	Summary of Key Findings	Comments
Schuler et al. 2005	Copper-beryllium alloy processing	Personal	Production of rod and wire Range: <0.01-7.80 µg/m^3 Median: 0.06 µg/m^3 <1% of samples were >2 µg/m^3 24% of samples were >0.2 µg/m^3 Production of strip metal Range: <0.01-0.72 µg/m^3 Median: 0.02 µg/m^3 <1% of samples were >2 µg/m^3 <1% of samples were >0.2 µg/m^3 Production support Range: <0.01-0.33 µg/m^3 Median: 0.02 µg/m^3 <1% of samples were >2 µg/m^3 2% of samples were >0.2 µg/m^3 Administration Range: <0.01-0.11 µg/m^3 Median: 0.02 µg/m^3 <1% of samples were >2 µg/m^3 <1% of samples were >0.2 µg/m^3	Sampling from 1977 to 2000
Stefaniak et al. 2003a	Department of Energy Los Alamos National Laboratory	Area and 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
Deubner et al. 2001a	Mining and mill facility Products facility Ceramics facility	Area	Mining and milling: 0.3-1.9 µg/m^3 (annual medians) Mining and 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 and 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 and 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 and breathing-zone samples
		Personal	Mining and milling: 0.05-0.8 µg/m^3 Mining and milling annual maximums: 0.04-165.7 µg/m^3	
Johnson et al. 2001	Cardiff Atomic Weapons Plant	Area	Annual mean range: 0.02 (in 1997) to 0.32 µg/m^3 (in 1985) Annual maximum range: 7.02 (in 1997) to 1,128 µg/m^3 (in 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 (in 1997) to 0.28 µg/m^3 (in 1984) Annual 95th percentile range: 0.22 (in 1997) to 1.1 µg/m^3 (in 1983) Overall mean foundry workers: 0.87 µg/m^3 Overall mean inspection workers: 0.22 µg/m^3 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	
Kelleher et al. 2001	Machining facility	Personal	Individual lifetime weighted exposure: 0.08-0.6 µg/m^3	20 workers with BeS or CBD
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 was 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 and beryllium fluoride reduction furnace had highest concentrations

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TABLE 2-5 *Continued*

Reference	Setting	Sample Type	Summary of Key Findings	Comments
		Area	Total mass mean range: 0.85-2.74 μg/m^3 Alveolar deposition: 0.02-0.29 μg/m^3	MOUDI Ammonium beryllium fluoride and beryllium fluoride reduction furnace had highest concentrations
Sanderson et al. 2001a	Beryllium plant in 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
Hennenberger et al. 2001	Ceramics plant	Area	1.7% of samples were >2 μg/m^3 0.6% of samples were >5 μg/m^3 0.2% of samples were >25 μg/m^3	Sampling from 1981 to 1998
		Breathing zone	6.4% of sample were >2 μg/m^3 2.4% of samples were >5 μg/m^3 0.3% of samples were >25 μg/m^3	
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	
Viet et al. 2000	Department of Energy 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 from 1960 to 1988
Yoshida et al. 1997	Beryllium-copper alloy plants	Area	Plant 1 alloy process: 0.16-0.26 μg/m^3 (GM range for 1992-1995); maximum: 1.85 μg/m^3 Plant 1 process without beryllium: 0.01-0.02 μg/m^3 (GM range for 1992-1995)	

			Plant 2 alloy cold rolling, drawing, and heat treatment: 0.03-0.19 μg/m^3 (GM range for 1993-1995); maximum: 0.28 μg/m^3 Plant 2 processes without beryllium: <0.01 μg/m^3	
Kreiss et al. 1997	Beryllium and 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 and 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, and personal samples
Barnard et al. 1996	Department of Energy 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
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 and grinding
Seiler et al. 1996	Various facilities (five plants in PA and 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)	

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TABLE 2-5 *Continued*

Reference	Setting	Sample Type	Summary of Key Findings	Comments
		Daily weighted average	Mean range: 0.3-4.8 µg/m^3	
Stange et al. 1996a	Department of Energy Rocky Flats, main production building	Area	Annual average range (1970-1988): 0.03 µg/m^3 (in 1987) to 0.42 (in 1973)	Based on random sample of results
		Personal	Annual average range (1984-1987): 0.19 (in 1987) to 1.2 µg/m^3 (in 1985)	
Stange et al. 1996b	Department of Energy 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	
Hoover et al. 1990	Sawing and milling of beryllium metal and alloys	Area	General work area: 0.07 µg/m^3 Ventilation shroud: >7,000 µg/m^3	Sawing, milling, and grinding produced large particles (50-300 µm) PCAM
Kriebel et al. 1988	Extraction and 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 Assume 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 in 1983
Cotes et al. 1983	Ore refining	Area	1952: 0.8 µg/m^3 (mean) 1960: 0.4 µg/m^3 (mean) Highest samples collected in final hydroxide plant in 1952 (2 µg/m^3) Only 9% of 3,000 samples exceeded 2 µg/m^3	
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 in 1974

		Personal total dust	Mean in powdered-metal products area: 1.02 ± 1.63 $\mu g/m^3$ (n = 105) Mean in extraction oxide area: 1.40 ± 1.26 $\mu g/m^3$ (n = 144) Mean in ceramics area: 0.75 ± 1.36 $\mu g/m^3$ (n = 36) Mean in alloy area: 1.58 ± 1.90 $\mu g/m^3$ (n = 54) Mean in maintenance area: 3.59 ± 9.85 $\mu g/m^3$ (n = 18)	
		Personal respirable dust	Mean in powedered-metal products area: 5.2 ± 10.73 $\mu g/m^3$ (n = 105) Mean in extraction oxide area: 2.63 ± 1.88 $\mu g/m^3$ (n = 144) Mean in ceramics area: 1.69 ± 3.06 $\mu g/m^3$ (n = 36) Mean in alloy area: 5.09 ± 6.75 $\mu g/m^3$ (n = 54) Mean in maintenance area: 12.96 ± 35.74 $\mu g/m^3$ (n = 18)	
Campbell 1961	High-explosives test facility	Area	Mean concentration inside bunker range: 0.08-0.14 $\mu g/m^3$ Mean in control room: 0.07 $\mu g/m^3$ Mean in office: 0.04 $\mu g/m^3$	Test explosions produced soil contamination extending up to 200 ft from test site.
		Breathing zone	Mean concentration outside bunker: 0.11-2.4 $\mu g/m^3$	
Mitchell and Hyatt 1957	Department of Energy Los Alamos National Laboratory	Area	98% of samples were <1.0 $\mu g/m^3$ 2% of samples were 1.0-25 $\mu g/m^3$	Machine shop sampling from 1952 to 1956, highly controlled environment
		Shop stack samples	6% of samples were 1.0-25 $\mu g/m^3$	
Sussman et al. 1959	Non-occupational	Ambient air sampling	Median around plant: 0.004 $\mu g/m^3$ Median around steel mill collected for comparison: 0.0002 $\mu g/m^3$	500 2-day samples collected around a beryllium plant in PA
Eisenbud et al. 1949	Non-occupational	Ambient air sampling and modeling	Concentrations 0.75 miles from the plant ranged from 0.004 to 0.02 $\mu g/m^3$	Based on investigations of berylliosis case near a beryllium processing plant in Lorain, OH

Note: GM = geometric mean, GSD = geometric standard deviation, PCAM = portable continuous aerosol monitor, TWA = time-weighted average.

Skin-Exposure Studies

A consistent inhalation-response relationship for CBD has been difficult to establish. Additional exposure matrices that have not been measured may contribute to the inconsistency. One possible additional exposure route is through the skin (Tinkle et al. 2003). Penetration of the skin by poorly soluble beryllium particles could provide an immunologic route to sensitization, as shown by earlier study with soluble beryllium salts (Curtis 1951). To determine whether skin could be a route of exposure to particles, such as beryllium, Tinkle et al. (2003) demonstrated that 0.5- and 1.0-μm particles in conjunction with motion, as at the wrist, penetrated the stratum corneum of 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) proposed that skin exposure may be sufficient to cause beryllium sensitization (BeS) but that inhalation exposure, even at concentrations below 2 $\mu g/m^3$, may be 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 ($r = 0.79$) and between beryllium on cotton gloves and on work surfaces (0.86), necks (0.87), and faces (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 continues to reach the skin of workers in production and production-support areas. Skin exposure is probably an important exposure pathway that can lead to sensitization and the development of CBD (see Chapter 3 for further discussion).

Only three studies, in addition to 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 inside vehicles and on the hands of machine-shop workers. The systemic toxicity of ingested insoluble forms (metal, alloy, and oxide) is thought to be low, but the role of ingested beryllium in sensitization is not clear.

The following can be tentatively concluded from the limited literature:

- Even in workplaces with stringent exposure controls, measurable amounts of beryllium on surfaces and the skin of workers can be detected.
- Surface and skin contamination appears to correlate with airborne beryllium concentration. Surface contamination can result in the spread of beryllium from primary production or use areas.
- Skin exposure is an important and underassessed route of exposure.

Biomarkers of Exposure

Two studies, one in workers (Apostoli and Schaller 2001) and one in the general population (Paschal et al. 1998), reported inconsistent results of using beryllium in urine as a biomarker of exposure (see Table 2-7). Metallurgy workers investigated by Apostoli and Schaller had urinary concentrations similar to those in the general population—on the basis of the National Health and Nutrition Examination Survey (NHANES)—reported by Paschal et al., whereas nonexposed controls in the Apostoli and Schaller population had exposures below detection and about one-tenth that in the NHANES sample. Urinary beryllium is not commonly used as a biomarker and is of uncertain utility.

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 ranged from below the limit of detection to 0.26 µg/100 cm^2 Postexposure samples for coverall surfaces ranged from 1.6 to 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 GM range: 0.05 µg/100 cm^2 (administrative area) to 13.6 µg/100 cm^2 (wire annealing and pickling area)	Large variability, GSDs range from 2.1 to 7.8 *n* = 252
		Cotton glove	Overall GM: 13.4 µg/glove GM range: 0.07 µg/glove (administrative area) to 196.5 µg/glove (rod and wire production area)	Strong positive correlations between air and surface, surface and glove, glove and skin
		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 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) were <0.01 µg/cm^2 Mean of four detectable samples was 3.5 µg/cm^3	

Note: GM = geometric mean, GSD = geometric standard deviation.

TABLE 2-7 Summary of Beryllium Biomonitoring Exposure Studies

Reference	Jobs or Worker Area	Sample Type	Summary of Key Findings	Comments
Apostoli and Schaller 2001	Metallurgy workers	Spot urine	Electric steel-plant furnace workers: 0.09 µg/L (median) Electric steel-plant casting workers: 0.06 µg/L (median) Copper-alloy foundry furnace workers: 0.25 µg/L (median) Copper-alloy foundry casting workers: 0.125 µg/L (median) Controls: <0.03 µg/L	End of shift Airborne and urinary beryllium strongly correlated
Paschal et al. 1998	General population	Urine	Median: 0.13 µg/L Mean: 0.22 µg/L	Creatinine-adjusted NHANES sample

REVIEW OF AIR-SAMPLING AND ANALYTIC METHODS

Beryllium-aerosol exposure-assessment methods have changed (Kolanz et al. 2001). The first air samples for beryllium were collected with electrostatic precipitators (Mitchell and Hyatt 1957). In the early 1950s, filter-based sampling was initiated (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 in the literature: fixed-airhead samples, high-volume samples, and personal samples (Hyatt and Milligan 1953; Campbell 1961; Lindeken and Meadors 1960; 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). Modern atomic-absorption spectroscopic methods of detecting beryllium were introduced in the 1970s and improved sensitivity to about 0.005 µg of beryllium.

EXPOSURE METRICS

The precise dose-response relationship between exposure to beryllium and development of CBD has remained unclear, probably because of both the uncertainty regarding beryllium exposure and the immune nature of CBD. Furthermore, the poor characterization of beryllium exposures 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 2-8 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

TABLE 2-8 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
Beryllium carbonate (basic)	$Be(CO_3)_2$	112.05	No data	No data	No data	Cold, insoluble; hot, decomposes
Beryllium hydroxide	$Be(OH)_2$	43.03	Decomposes (loses H_20)	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_20)	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

SOURCE: ATSDR 2002.

soluble in water. Beryllium carbonate and beryllium sulfate are formed in a step during the extraction of beryllium hydroxide from ore. Beryllium ammonium fluoride and beryllium fluoride are formed in steps of processing beryllium hydroxide to beryllium metal.

Concentration and Types of Beryllium in the Workplace

In this section, the concentrations and types of beryllium exposure in workplaces are described. Much of this information was ascertained as part of epidemiologic studies of BeS and CBD. More detailed discussion of these studies and the relationships found between BeS and CBD and specific exposures are discussed in Chapter 3.

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 also to mechanically resuspended particles from work surfaces and clothing fabric. Other factors, such as the ventilation system and use of local exhaust hoods, also influence exposure concentrations. A cross-sectional study in 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). However, no association between BeS and cumulative or average exposure to beryllium was found. It is possible that other physicochemical factors that potentially can influence bioavailability of beryllium—including particle size, specific surface area (SSA), and chemical composition—were more important than exposure concentration in determining disease outcomes.

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. When that information is combined with results of a simultaneous time and motion study of the worker, one can obtain an estimated time-weighted average (TWA). An average ratio of about 3:1 was found when exposure measured with personal lapel monitors was compared with exposure estimated using area monitoring and time-motion studies. Placement of the monitors, fluctuations in flow rate of the sampling pumps, and resuspension of dust from work clothing into lapel monitors contributed to the discrepancy (Cohen 1991).

The dose of inhaled dust in an industrial setting can be influenced by several factors, such as exposure 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 than did sawing (9% and 0.3%, respectively). 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 2-9 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 with more than 50% of the mass in the breathing zone of the worker consisting 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 with the mean MMAD of beryllium particles observed in various operations ranging 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 flowrate 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 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 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

TABLE 2-9 Comparison of Beryllium Concentrations and Particle Size Obtained with Different Operations in a Precision Machining Plant

	Point of Operation[a]		Near Worker Location[a]		Personal Impactor[b]		Total Be[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		0.11	1.2	0.13	2.3	0.31
Lathe operation	4.08		0.27	0.6	0.60	0.6	1.01
Milling	0.18		0.18	0.6	0.25	2.7	0.52

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

of particle-mass dose and particle-number dose. Because the majority of the epidemiologic studies of health risk of beryllium only measured 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 of 4.4; 95% confidence interval: 1.1, 17.6). The exposure concentrations at which workers developed CBD and BeS were mostly below OSHA'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 this is not statistically significant, the median cumulative total exposure was consistently higher in the cases (2.9 $\mu g/m^3$-years) than in the controls (1.2 $\mu g/m^3$-years). Median cumulative exposure of cases and controls to particles smaller than 6 µm in diameter was 1.7 $\mu g/m^3$-years and 0.5 $\mu g/m^3$-years, respectively.

Stefaniak et al. (2003b) investigated the contribution of particle structure and surface area as risk factors in CBD. Particles (powder and process-sampled) of beryllium metal, beryllium oxide, and copper-beryllium alloy 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 particles were clusters of smaller primary particles. 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 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 <6 µm) to 20.8 m^2/g (particles ≤0.4 µm). In contrast, little relative difference (<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 a 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 is inversely proportional to the temperature of calcination. 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 either 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 1,000°C, even though there was no difference in size or structure of the particles as a function of calcination 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 1,000°C. HCl increased the beryllium dissolution rate from what it was in SUF, and the beryllium oxide aerosol calcined at 500°C was more soluble than the 1,000°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 any of the beryllium forms dissolved in SUF, whereas more than 99% of the 500°C-calcined beryllium oxide aerosol, 50% of the 1,000°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 1,000°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 1,000°C elicited little local pulmonary immune response, because of its low solubility, 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, with maximal uptake after 6 h. The uptake was independent of calcining temperature. About 22% of 500°C 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 1,000°C 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 (Kreiss et al. 2007). 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 for the multiconstituent arc-furnace particles was greater than that for 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 these types of aerosols.

Because an oxide layer may form on beryllium metal surfaces upon exposure to atmosphere (Mueller and Adolphson 1979), Harmsen et al. (1984) have suggested that a sufficient rate of dissolution

of small amounts of poorly soluble beryllium compounds might occur in the lungs to allow persistent low-level beryllium presentation to the immune system. It is clear from these studies that more efforts are required to evaluate the role of intrapulmonary dissolution in beryllium-induced immune system stimulation and subsequent development of CBD.

SUMMARY

It is important to consider several exposure parameters in understanding the dose-response relationship between exposure to beryllium and the development of CBD. These parameters include airborne concentration, particle size, particle composition, and particle solubility. In addition, there is now evidence that skin exposure is probably an important contributor to sensitization. Thus, in the second report, the committee will focus its attention on characterizing inhalation and skin exposure contributions to risk of BeS and CBD, and whether differences in the physiochemical properties and bioavailability of beryllium compounds warrant the development of different chronic inhalation exposure levels for different beryllium compounds.

3

Sensitization and Chronic Beryllium Disease

It is well established that beryllium causes sensitization (BeS) and chronic beryllium disease (CBD). This chapter provides an overview of the literature relevant to assessing the risks of those conditions associated with occupational exposure to beryllium. We first review the epidemiologic literature on BeS and CBD. The current clinical description of CBD is presented next with diagnosis, testing, and management approaches. That is followed by a discussion of what is known about the pathogenesis and mode of action of CBD and about genetic factors that confer susceptibility to it. Finally, we consider the development of animal models to study CBD.

EPIDEMIOLOGY AND CLINICAL DISEASE

Exposure to beryllium 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 1930s, was observed in beryllium workers and was characterized by the onset of 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 recurrences occurred on repeat exposure (Van Ordstrand et al. 1945). Several fatalities were reported, and pathologic changes in those cases showed edema, infiltration with mononuclear inflammatory cells, alveolar cell proliferation or desquamation, and the absence of granulomas (Freiman and Hardy 1970). The incidence of acute beryllium disease decreased after respiratory exposures to beryllium were controlled in the plant (Van Ordstrand et al. 1945). The mechanism of a dose-related toxic pneumonitis has been postulated, although immune or hypersensitivity responses are also possible. Acute beryllium disease has rarely been reported over 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 also occur in other organs, such as skin, liver, and spleen. BeS precedes the development of CBD and is detected on the basis of the in vitro response of lymphocytes to beryllium in the beryllium lymphocyte proliferation test (BeLPT). Historically, CBD was diagnosed when it presented with progressive respiratory symptoms, such systemic complaints as fatigue, and radiographic and lung-function abnormalities. Screening healthy workers with the BeLPT has enabled the detection of BeS in asymptomatic exposed workers and the

earlier diagnosis of CBD and has changed the clinical spectrum of CBD. This section reviews the recent epidemiologic literature on BeS and CBD and their clinical presentation, diagnosis, and management.

Epidemiologic Literature

CBD was first reported in the United States in the early 1940s by Van Ordstrand et al. (1943), Kress and Crispell (1944), and 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 rose with the intensity of airborne exposure and that risk varied with the physicochemical properties of the beryllium exposure (Machle et al. 1948; see Chapter 2 for more information). From the late 1940s into the 1960s, there were also outbreaks of CBD caused by air pollution around beryllium refineries in Ohio and Pennsylvania and outbreaks in family members of beryllium-factory workers, presumably caused by contaminated clothing (Hardy 1980). Although there was a clear relationship between the air concentration of beryllium and the risk of CBD in areas close to the factories, the disease rates outside the plant were higher than expected (Eisenbud et al. 1949; Lieben and Metzner 1959).

The risk of CBD in workers exposed during the 1940s and 1950s has been estimated to be 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 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 surprisingly high risk in neighborhoods whose exposures 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 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 occurs 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 epidemiology studies from chest radiographs and spirometry to the identification of BeS with a blood test, followed up with biopsy as well as clinical examination. This change created a fundamental non-comparability in the clinical and epidemiology literature pre- and post-BeLPT development, which (along with reduced exposures) has been associated with identification of clinically milder cases of CBD compared with the older clinical and epidemiologic literature. There appears to be a consensus in the field that a case series of CBD identified in exposed workers by BeLPT and confirmed with biopsy provides more specificity in diagnosis compared with tools such as chest radiographs and spirometry. Unfortunately, there are no studies that formally document this impression. For this reason, in its review of the epidemiologic evidence, the committee decided to focus primarily on the epidemiologic studies of CBD that include the use of the BeLPT. The committee took into account the results of the older epidemiology studies along with clinical studies and case series describing clinically diagnosed CBD in the pre-BeLPT era to inform other sections of this chapter (see sections on "Presentation, Diagnosis and Testing of CBD" and "Natural History and Management").

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). Those data reflect exposures to workers decades after the recognition of the disease and indicate that many workers are still being exposed to concentrations of beryllium that put them at risk. The high

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 and 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 and 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 and 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 and former workers
Stange et al. 2001	Longitudinal	4.5%	1.6%	No	Current and former workers (including workers in Stange et al. 1996b)
Sackett et al. 2004	Cross-sectional	0.8%	0.1%	No	Decontamination and decommissioning workers only
Viet et al. 2000	Case-control	N/A	N/A	Yes	Current and former workers
Hanford Nuclear Reservation, Oak Ridge Reservation, and Savannah River site					
Welch et al. 2004	Cross-sectional	1.4%	0.1%	No	Construction-trade workers

[a]No = no evidence of exposure-response was provided by the paper; Yes = evidence of increased prevalence or risk with increasing exposure.

SOURCE: Adapted from Kreiss et al. 2007. Adapted table reprinted with permission; copyright 2007, *Annual Review of Public Health*.

prevalences of BeS and CBD in the studies by Kreiss et al. (1997, 1998), Henneberger et al. (2001), Newman et al. (2001), and Rosenman et al. (2005) are at least partly explained by higher ambient airborne concentrations of beryllium in these 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 strongly affected by the extent of followup of former workers, the time elapsed since initial exposures, and the physical form and intensity of exposure.

It is very difficult to estimate the "background" risk of CBD. Although there is natural background 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 limited use in estimating background risk. It is also likely that many cases of CBD are mistakenly diagnosed as sarcoidosis, and without a known source of exposure, and lacking a BeLPT, there is no way to distinguish these CBD cases from sarcoid.

The recent literature on BeS and CBD in different sectors of the beryllium industry is briefly summarized below. The division into sectors may be useful because it roughly corresponds 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 designs, number of study participants, how exposures were quantified, diversity of physicochemical form of beryllium, genetic susceptibility to CBD, and the healthy worker effect. In its second report, the committee will provide an expanded discussion of these issues 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 extracts beryllium from beryl ore (3.6-5.0% beryllium) that is mined abroad. A medical screening in 1996 included the BeLPT. Seventy-five of 87 (86%) workers in the facility were tested, and 12 refused to be tested. The single worker found to have CBD 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 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; Newman et al. 2001; Rosenman et al. 2005). The relevant studies involved cross-sectional screening of a working population, and each found both BeS and CBD (Table 3-1).

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. Those 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 was conducted on all workers, 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, 20 workers with BeS (n = 7) or CBD (n = 13) were compared with 206 at-risk workers who had neither condition in a case-control analysis (Kelleher et al. 2001). Exposure assessments for cases and controls were conducted 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 in 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 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 across three exposure groups; when compared with those who had low cumulative exposure (less than 0.09 $\mu g/m^3$), the odds ratio (OR) for those with medium exposure (0.09-1.87 $\mu g/m^3$) was 1.85, and for high exposure (over 1.87 $\mu g/m^3$) the OR was 2.46. Confidence intervals were rather wide because of the small numbers of cases, but a clear trend was evident.

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 them (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 associated with low exposure. The plant that still produces ceramics has monitored workers closely for the onset of sensitization (and for CBD among 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 of 136 screened workers (5.9%) 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 also carried out at the same time. Overall, 15 of 151 (9.9%) 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 the recently installed ventilation controls had not reduced the prevalence of sensitization, the company embarked on a second, much more elaborate control strategy, including careful attention to elimination of skin contact, stricter control of airborne exposures, and reduction of the resuspension of settled particles. 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 among those hired in 2000-2004 was 0.7 case per

1,000 person-months, and the incidence in the group hired earlier was 5.6 cases per 1,000 person-months. Again, although that is a large difference, it was based on very small numbers: one case in 1,480 person-months vs six cases in 1,081 person-months, respectively.

It appears from the Cummings et al. paper that an elaborate control program, including scrupulous attention to skin contact, inhalation exposure, and dust control throughout the facility, was effective at reducing (but not eliminating) the risk of sensitization. The 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).

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 the case subjects 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 relationships 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 these 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. 1993a,b, 1996) indicate that CBD can occur in workers exposed at well 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 refusals to participate, 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 prevalences of BeS were 0.8-11.8% and of CBD were 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 clinically diagnosed CBD.

Controls were chosen by 1:1 sampling and matching to cases on age, sex, race, and smoking. There were 74 cases of BeS without evidence of CBD and 50 cases of 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 very large, the samples were not taken in the workers' breathing zones but rather at fixed locations throughout the workplace. One would expect a certain amount of 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 fit to case-control status in logistic-regression models. There was strong evidence of increasing risk of CBD with increasing beryllium exposure, particularly as measured by 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 BeS

Only a few studies have investigated 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 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).

More recently surveillance studies of current and former workers at Rocky Flats have found that about 3.3% (172 of 5,173) of workers were sensitized to beryllium on initial screening; about 40% (74 of 172) of the sensitized workers were diagnosed with CBD (Stange et al. 1996b, 2001). Repeat evaluation of 2,891 workers 3 years later identified an additional 63 (2.2%) workers with BeS, seven of whom had CBD (Stange et al. 2001). Thus, 4.54% of screened workers had BeS. Machinists were at highest risk for CBD (11.4%). Additional long-term followup is needed to determine what proportion of the remaining workers with BeS will progress to CBD.

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 a positive BeLPT 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; machinists had the highest likelihood of progression to CBD. The authors estimated that BeS progresses to CBD at a rate of 6-8% per year after diagnosis. For a 6-year followup period, the progression rate was estimated at 3.2-9.2% per year. The likelihood of progression from BeS to CBD was associated with loss of lung function and the presence of a higher percentage of lymphocytes in BAL fluid than sensitized patients on baseline evaluation.

The longitudinal studies are consistent with the larger cross-sectional literature in showing that in most settings workers with BeS are at high risk for CBD but that the risk is variable.

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 some 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. Although they are considered "community cases," the exposures occurred before controls were instituted in the 1970s to reduce beryllium emissions into the air of surrounding communities, and some exposures were probably comparable with current occupational exposures or the "incidental" exposures noted above. It can also be difficult to rule out occupational exposure in some of those cases (Lieben and Metzner 1959; Dattoli et al. 1964; Lieben and Williams 1969; Newman and Kreiss 1992). On the basis of estimates of community exposure around one such plant, the U.S. Environmental Protection Agency set a community standard of 0.01 $\mu g/m^3$ in air averaged over a 30-day period (40 CFR Sec. 61.32).

Risk Posed by Skin Exposure

It has been presumed that the respiratory tract is the key route of exposure to beryllium, and research and prevention have focused almost exclusively on airborne exposure. However, BeS and CBD have persisted despite substantial reductions in respiratory exposures, and attention has recently focused on the role of skin exposure in BeS and CBD (Day et al 2007; Kreiss et al. 2007). As discussed above, several lines of evidence suggest that skin exposure may contribute to BeS and CBD and that reducing such exposure may reduce the risk of sensitization.

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 was developed as a diagnostic test for CBD but was discontinued because of concerns that such testing itself could cause BeS or worsen CBD (Curtis 1959).

The question of whether less soluble particulate forms of beryllium (metal, oxides, and alloys) that are the primary media of work exposure can penetrate human skin has been raised (see Chapter 2). An increased risk of CBD has been reported in workers who have skin lesions, which presumably 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).

The epidemiologic literature demonstrating weak relationships between air exposure and response and new cases of BeS and CBD despite reductions in air concentrations (to below the current standard of 2 $\mu g/m^3$) have been used to support a role of skin exposure in BeS (Henneberger et al. 2001; Cummings et al. 2007). Cummings et al. (2007) described the effects of a comprehensive prevention program in one beryllium oxide ceramics plant targeted at both respiratory and dermal protection (details of which were provided earlier in this chapter). The program included extensive 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, the rate of BeS was substantially reduced.

Most epidemiologic studies have not attempted to measure skin exposure for estimating exposure-response relationships, so the effectiveness of PPE is unclear. A recent exposure assessment at a copper-beryllium alloy facility documented beryllium contamination of work surfaces and gloves and exposure of skin on 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.

In addition to the beryllium literature, there is evidence 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; Day et al. 2007). The potential importance of skin exposure is also supported by the role of skin in the development of other systemic, as well as dermatologic, immune diseases.

For immune-mediated diseases, such as CBD and asthma, skin as a potential route of exposure and sensitization has several important implications for pathogenesis, risk factors, diagnosis, and prevention. 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 or eliminate the risk of disease.

Clinical Literature

There is a large body of clinical information on BeS and CBD. This section first reviews the literature on diagnosis of and testing for BeS; then 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 BeS

As described above, beryllium causes chronic granulomatous disease in the lung associated with the presence of lymphocytes that specifically respond to the presence of beryllium in the lung. Prior to the advent of the BeLPT, the diagnosis of CBD was based on clinical presentation and clinical diagnosis. In the 1970s and 1980s, researchers identified that lymphocytes from blood or the lung of individuals with CBD proliferated in the presence of beryllium in vitro. This response was refined and developed into what we know now as the BeLPT. The use of the BeLPT allows the identification of BeS in the absence of CBD.

BeS is not a disease in its own right and has no symptoms, but is important because it identifies a subgroup of exposed workers who are at risk of developing CBD. The diagnosis of BeS requires confirmation of an abnormal BeLPT with a second abnormal test. The BeLPT is now used as part of the diagnosis of CBD, for screening of asymptomatic workers or former workers for both BeS and CBD, and for surveillance to identify patterns of exposure to beryllium in the workplace.

The test involves an in vitro challenge of either BAL or peripheral blood lymphocytes with beryllium salts. In beryllium-responsive people, the challenge induces an oligoclonal proliferation of sensitized lymphocytes 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 do 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 after 3, 5, and 7 days in culture). Results are expressed as a "stimulation index": the ratio of the radioactivity counts per minute in cells stimulated by beryllium salts divided by the counts per minute in unstimulated cells. Each laboratory sets its own normal range for the test on the basis of data from normal nonexposed control subjects. A test is typically considered positive if two stimulation indexes are increased. The BeLPT, like other cell-culture assays, is associated with intratest, intertest, and interlaboratory variability; therefore, a positive, or abnormal, BeLPT result is generally confirmed with a second analysis, either by testing of the same blood sample in a different laboratory or by testing of a later sample before the subject is considered sensitized.

The BeLPT of peripheral blood or BAL cells is used as part of 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 lung diseases (such as sarcoidosis, chronic obstructive pulmonary disease, and hypersensitivity pneumonitis). Almost all 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. Thus, the BeLPT is very specific in this setting. Although some workers with an abnormal BeLPT do not have CBD, a confirmed abnormal blood BeLPT result is considered a strong predictor of CBD among workers with known exposure to beryllium. Several studies have reported that CBD is diagnosed in 50% or more of the screened workers with two abnormal blood BeLPT results (Newman et al. 2001). The conversion rate from BeS to CBD in one cohort of workers followed for a mean of 4.8 years was between 6% and 8% per year (Newman et al. 2005). More followup time is needed to see what the final lifetime risk is for this group. Nevertheless, the presence of BeS as measured with the blood BeLPT indicates a high probability of developing CBD in workers in beryllium production facilities.

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, 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 a higher agreement, 61.8%, but this rate 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.

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 immunosorbant spot assay (Pott et al. 2005) are under development.

Presentation and Diagnosis of and Testing for CBD

Clinically, CBD can be difficult to distinguish from sarcoidosis and other interstitial lung diseases, especially if, as is common, the history of beryllium exposure is not obtained. Since its pathogenesis involves a beryllium-specific, cell-mediated immune response, CBD cannot occur without sensitization. Thus, the clinical definition of CBD has evolved with the development of the BeLPT. Symptoms of CBD include dyspnea, cough, fatigue, anorexia, weight loss, chest pain, and arthralgia, or cases may be asymptomatic. Physical examination findings can be normal or include bibasilar crackles and, less commonly, lymphadenopathy, skin lesions, hepatosplenomegaly, and clubbing. Signs of pulmonary hypertension can be found in severe long-standing disease (Stoeckle et al. 1969). The clinical course of the disease can be variable. Systemic manifestations of CBD are less common than those of sarcoidosis and include increases in serum gamma globulin and erythrocyte sedimentation rate, erythrocytosis, hyperuricemia, and reversible hypercalcemia and hypercalcinuria. Renal calculi have also been reported (Stoeckle et al. 1969).

The current criteria for diagnosing CBD include all the following (Pappas and Newman 1993; Maier et al. 1999; Saltini et al. 2001; Amicosante et al. 2005):

- History of or evidence of beryllium exposure.
- Evidence of an immune response to beryllium, that is, positive responses in blood or BAL BeLPT tests or positive skin patch test (seldom performed in clinical practice). Those responses can also be considered evidence of exposure if exposure history cannot be ascertained.
- Nonnecrotizing granulomata on lung biopsy.

A clinical evaluation for CBD generally includes spirometry, measurement of lung volume and diffusion capacity, chest radiography, and, if clinically indicated, a high-resolution computed tomography

(HRCT) scan of the chest. For a person with a high likelihood of CBD or with abnormalities in the tests that suggest the presence of interstitial lung disease, the current clinical recommendation is to undertake BAL and transbronchial biopsy. In a clinical setting, the decision of whether to perform lavage and biopsy is made case by case. When a lung biopsy has not been done or is not possible, a presumptive diagnosis of CBD can be based on the presence of an immune response and radiographic findings (chest radiograph or HRCT scan) of diffuse small opacities.

CBD presents as a clinical spectrum in sensitized people that ranges from the presence of granulomas on lung biopsy without respiratory symptoms, radiographic abnormalities, or decrements in pulmonary-function or exercise tests to end-stage lung disease with severe dyspnea, severe pulmonary function changes, radiographic changes, arterial oxygen desaturation, and cor pulmonale. Between those extremes, there may be mild to severe changes in one or more of the tests. Many of the symptoms, radiographic changes, and pulmonary-function test findings in CBD are nonspecific and can be due to other conditions, so other explanations of such findings need to be considered. Conversely, pulmonary-function test results that are considered normal on the basis of predicted values in a patient with CBD may not be truly normal for that person and could reflect a substantial decline in lung volumes or carbon monoxide diffusing capacity (DLCO) in the person but still fall above the lower limit for "normal." Such changes may be apparent only if serial pulmonary-function test results are available with a true baseline for the patient. Thus, it can be difficult to determine whether mild disease is truly "subclinical" or constitutes a clinically significant effect; although the term *subclinical CBD* has been used (Kriebel et al. 1988; Newman 1996), it has not been clearly defined, and other terms have also been used, such as *early CBD* (Rossman 1996) and *surveillance CBD* (Pappas and Newman 1993).

Histopathology

The largest study of the histopathology of CBD examined 124 cases of CBD from the Beryllium Case Registry (Freiman and Hardy 1970). Patterns of diffuse noncaseating granulomas with various degrees of mononuclear-cell interstitial infiltrates were described in the lung-biopsy specimens from those patients. Giant cells, asteroid bodies within giant cells, and calcific inclusions were also noted. About half the cases had accompanying moderate to advanced interstitial fibrosis. The authors reported that patients with slight or absent cellular infiltration and with well-formed granulomas appeared to have a better prognosis. More recent studies have confirmed the histopathologic pattern of noncaseating granulomas, mononuclear-cell interstitial infiltrates, and interstitial fibrosis in lung specimens from transbronchial biopsies of patients with CBD (Newman et al.1989). The pathologic findings are not specific for CBD and may occur in other lung diseases, including sarcoidosis. 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, BAL, and Biopsy

Bronchoscopy with BAL and transbronchial biopsy is generally recommended for diagnosing CBD but is not without risk. Transbronchial lung biopsies are performed to determine the presence of nonnecrotizing granulomas and interstitial infiltration; fibrosis and coalescence into nodules 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). Biopsy samples should be stained to exclude infection.

BAL 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 on the BAL

cells (rapid processing of the fluid with a specialized technique is needed) (Rossman et al. 1988; Newman et al. 1989).

BAL typically shows lymphocytosis with varied percentages of lymphocytes (Rossman et al. 1988; Newman et al. 1989). The percentage of BAL lymphocytes may correlate with physiologic and radiographic disease severity. In some cases of subjects with BeS and biopsy-confirmed CBD, BAL may show 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 (Newman et al. 2005).

Pulmonary-Function Testing

Results of pulmonary-function testing in patients with CBD are variable; they include showing 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 exercising (Pappas and Newman 1993) and an increased alveolar-arterial oxygen (A-a) gradient on exercising (Daniloff et al. 1997), both reflecting impaired gas exchange. 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 air-flow rates but reduced DLCO) (36%), and an obstructive defect (39%); 5% were normal. 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.

A 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 per liter of alveolar volume (VA). The 11 with abnormal exercise physiologic results showed either increased V_D/V_T on exercise, abnormal gas exchange, or both. The 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, their DLCO/VA was lower, and they showed evidence of reduced exercise tolerance in addition to abnormalities in V_D/V_T and gas exchange.

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 scanning of the chest is more sensitive than plain chest radiography in identifying abnormalities in patients with CBD. However, HRCT scans showing no signs consistent with CBD have been reported in 25% of patients with biopsy-proven noncaseating granulomas (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. 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). Another proposed biomarker is beryllium-specific cytokine-secreting T cells (secreting IFγ and IL-2) that are detected in peripheral blood in an enzyme-linked immunosorbent spot assay (Pott et al. 2005). Such T-cell cytokine assays may help to differentiate BeS from CBD (Tinkle et al. 1997). Another proposed approach has been the use of induced sputum as an alternative to BAL fluid (Fireman et al. 1999), but the data are insufficient to evaluate this.

Natural History and Management

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 the asymptomatic form to functionally significant lung disease. The risk factors and time course have not been clearly delineated. Progression from asymptomatic to symptomatic disease in people now under surveillance has been suggested to be generally slow. Possible risk factors for progression that have not been systematically assessed include smoking status, race, sex, genetic factors, exposure duration, magnitude and type of beryllium exposure (including particle size and solubility), concurrent exposures, and life stresses, such as pregnancy and lactation, combat, and surgery (Newman 1996). Newman (1996) emphasized the need for prospective studies of the natural history of BeS and subclinical CBD. In his clinical experience, the sequence of events for those with progression has been from BeS to gradual emergence of chronic inflammation in the lung, pathologic alterations, measurable physiologic derangement (demonstrated by pulmonary function and gas exchange), more severe lung disease, and finally death in some cases. Rossman (1996) also reported that in his clinical practice an annual assessment of CBD patients is performed that includes a history, physical examination, chest radiography, pulmonary-function tests, and exercise-physiology tests to detect early lung damage. In a cohort of 55 patients with BeS followed for 1-11 years, 31% developed CBD in an average of 3.8 years (range, 1-9.5 years), but only one received oral steroid therapy, suggesting that most cases had generally mild disease in this time period (Newman et al. 2005). Longer followup will be needed to determine outcome for those with surveillance-detected CBD on a long-term basis.

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 (those 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 to management is periodic re-evaluation to look for deterioration in symptoms, pulmonary-function test results, or chest radiographs, typically every 1-2 years. 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 much 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 severe 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 commun., April 23, 2007).

There is also an absence of published data on socioeconomic effects of sensitization and disease. Recommendations have been made that sensitized people minimize further occupational exposure to beryllium (Infante and Newman 2004), and published recommendations have advised avoidance for those with CBD. Implementation of those recommendations might be expected to result in job loss or reduction in income. In addition, even for those without clinical disease, the diagnosis of subclinical 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 subclinical disease that resulted in job loss, major reactive depression, and unemployment (S. Tarlo, University of Toronto, personal commun., April 23, 2007). However, evaluation of the psychosocial and socioeconomic implications of receiving a diagnosis of BeS or subclinical disease is beyond the scope of the present committee's task.

Extrapulmonary Disease

Like sarcoidosis, CBD can have extrapulmonary manifestations; they are less common than in sarcoidosis, but few studies have systematically characterized them. Patch testing with soluble beryllium salts has confirmed skin sensitization to beryllium, and skin lesions were 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 almost exclusively on BeS or CBD and given little attention to skin symptoms and disease.

Surveillance of Beryllium-Exposed Workers with the BeLPT

When used on a population basis, rather than as a screening or diagnostic test, the BeLPT has been shown to be useful for identifying facilities or jobs that pose substantial risk. Medical surveillance with the BeLPT appears to be more sensitive than traditional air sampling because BeS can occur at extremely low air concentrations and also possibly from skin exposure, for which there are no standard monitoring or regulatory guidelines (Stange et al. 2004; Day et al. 2006; Kreiss et al. 2007).

Any test that is used in medical surveillance needs to have acceptable sensitivity, specificity, and predictive value. Since a diagnosis of BeS is usually followed by additional diagnostic testing for CBD with attendant risk and expense, such a diagnosis must have an acceptable positive predictive value (PPV) and so a limited number of false positive tests. 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 a blood sample was 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 the second laboratory. Because a diagnosis of BeS can lead to additional testing, including biopsy, the clinical definition of sensitization requires a confirmation of an abnormal BeLPT with a second abnormal test (a "confirmed abnormal"); this reduces sensitivity while raising specificity. A "false positive" diagnosis of BeS would then only occur if the BeLPT were confirmed abnormal. An unconfirmed abnormal BeLPT is not a false positive using this definition. It is theoretically possible that someone could have a confirmed abnormal BeLPT but not be sensitized to beryllium, but there is no other test to measure sensitization to beryllium, so it is not possible to identify these cases with any confidence. The available evidence suggests that such false positives are rare. For example, of 458 employees at Rocky Flats who were either new hires or standing employees with no known exposure to beryllium, none had a confirmed positive result (Stange et al. 2004). Silveira et al. (2003) combined data on three sites and found no confirmed positive results in over 1,000 "unexposed" people screened. Any estimate of the rate of a confirmed abnormal BeLPT in people with no exposure to beryllium is confounded by the fact that CBD (and hence a sensitivity to beryllium) has been found after relatively low exposures, and that there is no independent measure of beryllium exposure. If a person with no known exposure to beryllium has a confirmed positive BeLPT, might it be possible that he had occult exposure? Or if a job is thought to involve beryllium exposure in part because of surveillance using the BeLPT, might that job be inappropriately classified with a "false positive" BeLPT? The committee will address such questions in the second report, as part of the discussion of the usefulness of the BeLPT for medical surveillance.

The ultimate question is how well the BeLPT predicts CBD. 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, a test whose sensitivity is 99.9% and whose specificity is 99.9% is an excellent test. If we use this test in a population of 1,000,000 of whom 1% have the disease for which we are screening, we will detect 9,990 with the disease and miss 10 with the disease. 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. 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 test had a PPV for CBD of 39%, a confirmed abnormal result had a PPV for CBD of 45%, and a split sample reported as abnormal in two laboratories had a PPV of 49%.

Those results came from populations of workers with on-going exposure to beryllium. Some studies suggest that as exposure declines the incidence of sensitization may decline less than the incidence of CBD in a population; this would mean that the predictive value of the blood BeLPT for CBD may be

lower in workers with low or intermittent exposure to beryllium than in the populations discussed above. Stange et al. (2001) described the prevalence of BeS and CBD in workers at Rocky Flats tested through on-going beryllium surveillance. As years of exposure increased, the proportion of those examined who had CBD also increased, but the proportion of sensitization without CBD did not increase. The CBD prevalence increased from 0.5% in male workers with less than 5 years of employment to 3.7% in those with 20-25 years of employment. The prevalence of sensitization without CBD was 3% in workers with less than 5 years at the plant and was at most 4% in groups with more years of exposure. The ratio of people with CBD to all sensitized people (with and without CBD) is the PPV of the BeLPT; because there can be a long latency between BeS and CBD, the ratio will change with increasing length of followup. Overall, the PPV was 35% in the Rocky Flats workers described by Stange et al.; about one-third of those who were sensitized also had CBD. The PPV was 14% in workers with less 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 incidence of CBD varied among groups; for example, it was 23% in the scientists and engineers who were sensitized and 73% in the machinists.

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. The 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 that are manifested as disease in some people 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 3-1). In this context, $CD4^+$ 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 stimulating 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 lung is associated with the accumulation of $CD4^+$ T cells in the 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 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).

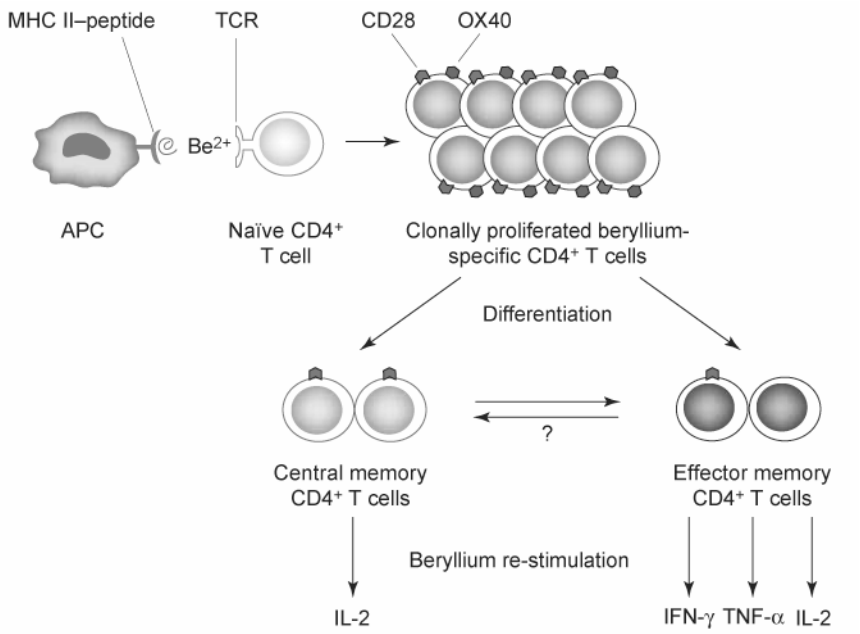

FIGURE 3-1 Immune response to beryllium. Source: Fontenot and Maier 2005. Reprinted with permission; copyright 2005, *Trends in Immunology*.

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 of 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.

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 with mouse lymphocytes, Newmann and Campbell (1987) reported that beryllium sulfate was mitogenic for B lymphocytes but not T lymphocytes. The potential for endotoxin contamination of the beryllium-salt preparation to drive this polyclonal B-cell response was not addressed by Newmann and Campbell. 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 physiochemical properties of beryllium ions offer few clues that lead 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 occupying 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 involved in all cases are different than those attributed to immune reactivity to beryllium. As with these immune reactivities to other metal:pMHC, the response to beryllium:pMHC is exquisitely specific and lacks crossreactivity with other metal:MHC complexes.

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 possessing a negatively charged glutamic acid residue at the 69th position of the β chain were especially capable of inducing a T-cell response (Richeldi et al. 1993; Wang et al. 1999; Lombardi et al. 2001; Fontenot et al. 2000; Bill et al. 2005). Not all CBD patients have a Glu69 containing HLA-DP allele. Indeed, the 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 lacking a Glu69 HLA-DP allele. These HLA-DR13 alleles possess a glutamic acid at position 71 of the β-chain (which corresponds to position 69 of HLA-DP). Beryllium presentation to $CD4^+$ T cells can occur through an alternate HLA-DR Glu71 pathway that is capable of inducing beryllium-specific proliferation and 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 requires 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 as well as at a pH of 7.5. The pH 5.0 mimics the acidic microenvironment where peptides are loaded onto HLA class II molecules, whereas, pH 7.5 represents the extracellular pH 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 to the cell-mediated immune reaction characteristic of beryllium disease. The physiochemical state of beryllium (i.e., single constituent versus multi-constituent material) influences its bioavailability, which may be tied to its ability to initiate or sustain immune reactivity to beryllium. Stefaniak et al. (2006) found that the dissolution rate stimulated by phagolysosomal fluid was greater for beryllium-copper-alloy fume than for

beryllium oxide, suggesting that the physiochemical 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 uptake 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 commun., 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 IL-2, IFN-γ, and 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 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 MIP-1α and GRO-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 to the perpetuation of granulomatous inflammation seen in CBD.

Beryllium-Sensitization Progression to Chronic Beryllium Disease

The immunologic mechanisms underlying the progression from 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 lung.

As mentioned above, the development of granulomatous inflammation in the lung 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 lung.

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 lung and the peripheral blood of CBD patients (Fontenot et al. 2003). These 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 (i.e., 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 BeS people. 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 earlier in this chapter, not all people exposed to beryllium become sensitized, and not all who do progress to develop CBD. Development of CBD appears to depend not only on the history of exposure to beryllium but also 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 classical 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 those 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, respectively, 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 3-2). 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 (Salitini 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 without 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, co-exposure 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 with 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, 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 appeared lower 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. However, 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 the more common 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 BeS and CBD groups, respectively. Maier et al.

TABLE 3-2 Summary of Association Studies on HLA-DPB1 Glu69 and TNF-α As Susceptibility Factors in Chronic Beryllium Disease and Beryllium Sensitization

Author		N	Frequency	Homozygocity	Alleles
HLA-DPB1 Glu69					**Glu69**
Richeldi et al. 1993	CBD	33	97%	N/A	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%	N/A	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 (data not shown)	Non-0201: associated with CBD vs. controls
	BeS	30	90%		
	Controls	82	47%		
Maier et al. 2003	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%	N/A
	BeS	64	68%	16%	
	Controls	727	33%	4%	
TNF-α-308					**Other Polymorphisms**
Saltini et al. 2001	BeS and CBD	45	51%		N/A
	Controls	93	16%		
Dotti et al. 2004	BeS and 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%	N/A
	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,
	BeS	112	36%	2.5%	-238; all not associated
	Controls	323	30%	2.3%	vs. controls

(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 (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 that because the HLA-DPB1 Glu69 genotypic distribution among CBD cases did not conform to Hardy-Weinberg population laws but did for BeS and controls, 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. Further complicating the issue is 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 (workers with 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 a significant number of 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 (TNF-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). (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" (n = 20) or "low" (n = 10) 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 those 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 also observed for another polymorphism, TNF-857T. 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; Amicosanti 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 (n = 147), BeS subjects (n = 112), and healthy beryllium-exposed controls (n = 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 the BeLPT. Gaede et al. (2005) did find an association between polymorphisms in the transforming growth factor β1 (TGF-β1) gene and CBD; the polymorphism was found in 59 CBD patients compared with 164 healthy beryllium-exposed controls. 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

Beginning in the early 1950s, numerous studies in several animal species were conducted with beryllium in different chemical forms and administered by different routes.

Hall et al. (1950) repeatedly exposed six species (cats, dogs, guinea pigs, monkeys, rabbits, and rats) to four types of beryllium oxide powders that varied in calcination and chemical form—$BeSO_4 \cdot 4H_2O$ fired at 1,350°C, $BeSO_4 \cdot 4H_2O$ fired at 1,150°C, $BeO \cdot 2H_2O$ fired at 1,150°C, and $Be_4O(C_2H_3O_2)_6$ fired at 400°C—in a dust-dispersion chamber. Hematologic and pulmonary effects of all the test agents in all the species were observed. Rats showed the highest acute toxicity. Beryllium oxide fired at 400°C was the most toxic, probably because of its small particle size (mass mean of 3 μm) and more extensive distribution.

Stokinger et al. (1950) tested 11 species with repeated 6-h exposures to beryllium sulfate at 1-100 mg/m^3 in inhalation chambers. Concentrations of 50 mg/m^3 and greater were lethal in most of the species. Two response phases seemed to occur: an acute phase, in which animals died within days or weeks, and a delayed phase, in which animals showed increasingly severe changes (anemia, weight loss, and histopathologic lesions in the lungs) over months that sometimes resulted in death.

In a study of female rhesus monkeys (Schepers 1964), beryllium fluoride was found to be more toxic than beryllium sulfate or beryllium phosphate. Weight loss, apathy or malaise, dyspnea, and death from chemical pneumonitis were reported. Pulmonary inflammation, edema, and emphysema were also evident.

Robinson et al. (1968) examined lung histopathology in two dogs exposed to dusts containing a mixture of beryllium oxide (50%), beryllium fluoride (40%), and beryllium chloride (10%) at 115 mg/m^3 for 20 min. Small perivascular granulomatous lesions were detected in the lungs after 3 years. The lesions were said to be typical of a foreign-body reaction.

The possibility that adrenal cortical imbalance (an effect sometimes triggered during pregnancy, surgery, or infection) can induce CBD was investigated by Clary et al. (1972). The distribution of radioactive beryllium oxide and beryllium sulfate instilled in the lungs of guinea pigs (strain 13 and albino) and mice (albino) was evaluated after treatment with metyrapone, a disruptor of corticosteroid synthesis (inhibition of 11β-hydroxylation). When adrenal function was altered, there was increased accumulation of beryllium in the liver and decreased accumulation in bone. Effects were greater in male mice than in female mice.

Clary et al. (1975) used beryllium oxide to examine the effect of adrenal stimulation caused by multiple pregnancies on the onset of CBD in male and female rats. The absence of an effect on beryllium oxide distribution or on the onset of CBD suggested that adrenal stimulation does not play a role in CBD.

Marx and Burrel (1973) found that Hartley guinea pigs could be sensitized to beryllium sulfate by repeated—but not single—intradermal injections, which led to positive skin tests. Migration-inhibitory-factor (MIF) production was correlated with positive skin tests, and it was suggested that reactivity to beryllium is associated with classic delayed hypersensitivity.

Eskenasy (1979) sensitized rabbits with intramuscular injections of 10 mg of beryllium sulfate in Freund's adjuvant. Intradermal and intratracheal challenges led to skin and lung granulomas, respectively.

In another study, rabbits intradermally immunized with beryllium sulfate (100 μg) developed delayed hypersensitivity reactions and skin granulomas when challenged (1-10 μg). MIF production in BAL cells was increased at doses of 5 and 10 μg. Beryllium was toxic to macrophages at doses greater than 10 μg. Popliteal lymph nodes were negative for beryllium-induced lymphocyte proliferation (Kang et al. 1977).

Barna et al. (1981) induced granulomatous lung disease in Hartley and strain 2 guinea pigs by administering injections of 10 mg of beryllium oxide intratracheally. Blood lymphocytes showed significant blast transformation when challenged with beryllium sulfate. Tolerance to the responses was achieved with intravenous or oral exposure to beryllium sulfate. The response was also mitigated by treatment with prednisone, L-asparaginase, or cytoxan. Sensitized guinea pigs had positive delayed-

hypersensitivity skin tests. Granulomatous lung disease was not induced by beryllium oxide in strain 13 guinea pigs; it was suggested that strain 2 animals had a genetic predisposition.

Goel et al. (1980) fed male albino rats 20 mg of beryllium nitrate every 3 days for 10 weeks. The lungs of exposed rats had histopathologic changes indicative of granuloma and inflammation.

Hart et al. (1984) examined the biochemical, cytologic, and histologic alterations in the lungs of F344 rats exposed for 1 h to an aerosol of beryllium oxide fired at 560°C. The initial lung burden of beryllium was 500 ng. Lung inflammation was detected by day 2. In BAL fluid, lipids, enzymes, and total proteins were increased and macrophage phagocytosis was reduced.

Increases in lactate dehydrogenase, alkaline phosphatase, acid phosphatase, and albumin were found in the BAL fluid of male F344 rats and Balb/C mice exposed nose-only to beryllium sulfate for 1 h (rats at 3.3 or 7 μg/L and mice at 7.2 μg/L). Time-dependent increases in those markers of lung damage were observed. Lactate dehydrogenase peaked on day 8 in rats and on day 3 in mice, and albumin peaked on day 5 in both species (Sendelback and Witschi 1987).

Votto et al. (1987) examined a rat model for beryllium sulfate-induced granulomas by using an ovalbumin and Freund's adjuvant emulsion. F344 rats were immunized with beryllium sulfate and then given subcutaneous booster injections every 2 weeks. Pulmonary granulomas surrounded by lymphocyte cuffs were found after 6 weeks. Immunohistochemical study of lung tissue showed an increase in helper-T subsets and B cells. Lymphocyte populations in BAL fluid did not correlate with those in lung tissue.

Sendelbach et al. (1989) examined histopathologic changes in male rats exposed nose-only to beryllium sulfate for 1 h at 4.05 μg of beryllium per liter. Focal interstitial pneumonitis was detected with an increase in interstitial and alveolar macrophages. Enzyme activity in BAL fluid was increased for up to 3 months and appeared to correlate with the severity of histopathology.

Several lines of research were pursued at the Inhalation Toxicology Research Institute to develop animal models of beryllium-induced lung disease (see Finch et al. 1996 for an overview). Haley et al. (1989) developed a beagle model of beryllium-induced granulomatous lung disease with beryllium oxide calcined at 500°C or 1,000°C. Lung burdens of beryllium achieved were 18 and 42 μg/kg for the 500°C beryllium and 18 and 48 μg/kg for the 1,000°C beryllium. Peribronchiolar and perivascular changes in the lungs that progressed to microgranulomas and granulomatous pneumonia were observed. The changes were more severe in dogs exposed to the 500°C beryllium. The percentages and total numbers of lymphocytes in BAL fluid were increased after 3 months in dogs treated with 500°C beryllium but not in dogs treated with 1,000°C beryllium. Peripheral blood lymphocytes responded to beryllium challenge in vitro in all four treatment groups after 6-7 months, but positive results for lung lymphocytes were observed only in the group with high lung burdens of 500°C beryllium. The granulomatous lung response was reported to be similar to that observed in humans, but the responses 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 2.5 years after the first exposure to achieve lung burdens of 17 or 50 μg/kg. Lung pathologic effects, particle clearance, and immune sensitization of peripheral blood leukocytes were monitored. Beryllium-induced proliferation of blood lymphocytes was noted from day 30. Inconsistent results were observed with lung lymphocytes cultured with bovine serum, but when cells were cultured with dog serum, increases in blood and lung lymphocytes were observed. The authors concluded that "[beryllium]-induced granulomatous and fibrotic lung lesions are accompanied by [beryllium]-specific immune responses within the lung but these changes do not appear to be cumulative if enough time has elapsed between exposures" (p. 400).

Haley et al. (1990) studied the acute toxicity of beryllium metal after a single nose-only exposure of F344 rats (at 800 $\mu g/m^3$ for 50 min). Rats developed acute, necrotizing, hemorrhagic, exudative pneumonitis and intra-alveolar fibrosis that peaked on day 14. BAL fluid had increased numbers of inflammatory cells and enzyme concentrations. 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 (inflammation and alveolar epithelial hyperplasia) was 1.8 μg. At burdens of 10 and 100 μg, particle clearance from the lung was reduced, and pulmonary inflammation was 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 general increases in total numbers of cells, neutrophils, proteins, and enzymes.

Mouse models of beryllium-induced pulmonary granuloma were investigated by Huang et al. (1992). A/J mice were immunized with three subcutaneous injections of 5-50 μg of beryllium sulfate in syngeneic serum, bovine serum albumin, or Freund's adjuvant and then intratracheally challenged with 1-5 μg of beryllium sulfate. Granulomas were found only in mice treated with beryllium sulfate in syngeneic serum. Microgranulomas were observed after 4 weeks, and granulomatous lesions and perivascular lymphoid accumulations were seen after 8 weeks. However, those lesions regressed within 20 weeks. Inflammatory cells, especially Mac-1-positive macrophages, were increased in the BAL fluid. T cells mediating delayed hypersensitivity were also detected after 1-8 weeks. In vitro evidence of BeS was found only in mice sensitized with beryllium sulfate in serum. Similar experiments with beryllium sulfate in BALB/c and C57BL/6 mice did not produce any lung granulomas, nor were granulomas induced in nonimmunized mice treated with a single intratracheal instillation of beryllium oxide.

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 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 immune granulomas. Lesions were found less frequently and were less severe in monkeys treated with beryllium oxide.

Nikula et al. (1997) demonstrated chronic granulomatous pneumonia and lymphocytic responses induced in A/J and C3H/HeJ mice by inhalation of beryllium metal (at 1,030 mg/m^3 for 90 min). Granulomas, epithelial hyperplasia, and inflammatory cells were detected in the lungs of both strains of mice at 28 weeks. T-cell proliferation responses in the spleen, lymph nodes, and peripheral blood evaluated in vitro did not differ between beryllium-treated and control mice. There was an increase in CD4+ cells in the lungs of treated mice. The authors suggested that their model of CBD was associated with T-cell delayed hypersensitivity and not a foreign-body reaction that is seen in rats.

Pfeifer et al. (1994) compared the histopathologic findings of sarcoidosis and berylliosis in F1 mice (C57BL/6 × DBA/2) given intraperitoneal injections of beryllium sulfate at 3 mg/kg. There was an increase in the formation of reactive oxygen intermediates by murine peritoneal exudate cells and a decrease in T-cell responses to concanavalin A by spleen cells. The authors concluded that although no granulomas were detected, there were similarities between sarcoidosis and beryllium disease in that macrophages were activated in the peritoneum and there was systemic immunosuppression.

Finch et al. (1998a) exposed C3H/HeJ mice to beryllium-metal aerosols to achieve lung burdens of 1.7-34 μg. Particle clearance was impaired at 12 and 34 μg through day 196. Increased numbers of inflammatory cells and enzyme concentrations were detected in the BAL fluid of mice with the two highest lung burdens (12 and 34 μg). Granulomatous pneumonia was seen histologically beginning on day 8 in the high-dose groups and on day 15 in the 2.6-μg group.

Benson et al. (2000) performed biodistribution studies in C3H/HeJ mice given particles of beryllium metal or beryllium-copper alloy (2% beryllium, 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 the metallic beryllium powder suggested copper toxicity. Pulmonary clearance of beryllium was found to be much slower than clearance of copper.

Because mice do not have susceptibility alleles equivalent to those found in humans, new knock-in mouse models with human alleles associated with a range of BeS/CBD risk are being developed that may be useful in experimental study of beryllium dose-response, beryllium type and characteristics conferring risk, dose rate, and therapeutic approaches to beryllium disease.

SUMMARY

Historically, CBD is the noncancer health end point on which occupational exposure limits are based. The epidemiologic evidence shows that the long-standing limit of 2 $\mu g/m^3$ is inadequate for preventing CBD. The studies have also shown that the risk of CBD in workers depends on the industry, process, and physicochemical form of beryllium being handled. In general, BeS should be regarded as an early marker of disease that is likely to progress to CBD, although the timing and probability of progression are not well-defined. There is growing evidence that skin exposure may be an important contributor to sensitization and development of CBD.

The use of the BeLPT and worker surveillance programs now allow earlier identification of people who are sensitized and who are at risk of CBD. It is clear from animal and human data that susceptibility to CBD has a genetic component and, as noted in Chapter 2, the physiochemical properties of the beryllium and the route of exposure also play a role.

There are currently no adequate animal models of CBD. However, efforts are under way to create mouse models with human alleles associated with a range of BeS and CBD risk that may be useful in experimental study of beryllium dose-response, beryllium type and characteristics conferring risk, dose rate, and therapeutic approaches to beryllium diseases.

In its second report, the committee will evaluate critical health end points on which to base chronic inhalation exposure levels, and consider how susceptibility to CBD should be factored into a risk assessment. The committee will also discuss aspects of the use of the BeLPT in routine surveillance and medical monitoring, including the value of the BeLPT in predicting CBD, protocols for further followup tests after a positive BeLPT result, the likelihood of developing CBD after a true positive test, and a standardized method for achieving consistent test results in different laboratories.

4

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 air unit risk of 2.4×10^{-3} per $\mu g/m^3$. This chapter examines the literature used in the previous assessments, more recent reviews, and relevant new studies. First, information on the genotoxic potential of beryllium and beryllium compounds is presented. The literature on carcinogenicity, including the epidemiologic literature and animal bioassays, is then reviewed.

GENOTOXICITY

Compounds of beryllium have tested positively in nearly 50% of the genotoxic 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 4-1) (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 *S. typhimurium* host-mediated assay (Simmon et al. 1979a), 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 for beryllium sulfate in the *B. subtilis* rec assay (Kada et al. 1980; Kanematsu et al. 1980) and the *E. coli* rec assay (Dylevoi 1990), for beryllium nitrate in the *B. subtilis* rec assay (Kuroda et al. 1991), and for 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

TABLE 4-1 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; Arlaukas et al. 1985; Ashby et al. 1990
	S. typhimurium	$Be(NO_3)_2$	Negative	Negative	Arlaukas 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
	Mouse macrophage $P388D_1$ cells	$BeSO_4$	—	Negative	Andersen 1983
DNA repair	Rat hepatocytes	$BeSO_4$	—	Negative	Williams et al. 1982, 1989

Continued on next page

TABLE 4-1 *Continued*

Assay or End Point	Species	Compound	With Activation	Without Activation	Reference
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

Note: Be = beryllium, $BeCl_2$ = beryllium chloride, $Be(NO_3)_2$ = beryllium nitrate, BeO = beryllium oxide, $BeSO_4$ = beryllium sulfate.
SOURCE: Adapted from ATSDR 2002.

mammalian cells cultured with beryllium chloride (Vegni-Talluri and Guiggiani 1967; Hsie et al. 1979; Miyaki et al. 1979) and beryllium sulfate (Larramandy 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. Further studies would confirm the mutagenic or genotoxic properties of the various beryllium compounds.

CARCINOGENICITY

Epidemiologic Studies

Several studies and reviews are available on cancer in relation to beryllium exposure in humans. Two worker cohorts involved in beryllium extraction, production, and fabrication have been extensively studied and are the primary basis of conclusions drawn to date on cancer in humans. One cohort is in Lorain, Ohio, and the other in Reading, Pennsylvania. The original study (Mancuso 1979) reported a lung-cancer standardized mortality ratio (SMR) for 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 through 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. The exposures of the workers were often at high concentrations. For example, a study at the Lorain 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 operatives (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 through 1948 and used workers at the rayon plant for comparison purposes. The comparison between the two types of industrial workers found a significant relative SMR for lung cancer 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 through 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 for the group that had a latency of 25 years or longer. However, there was no relationship with duration of employment. The results of a 1968 medical survey of smoking histories of the workers showed that differences in smoking habits were sufficient to increase the cancer risk among 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. In the study, Ward et al. (1992) developed a cohort of 9,225 male workers who had worked for at least 2 days during 1940 through 1969 and were followed through 1998. The SMR for lung cancer 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, with a significant SMR of 1.46 for a latent period greater than 30 years among the workers at the combined seven plants. The SMR for lung cancer was a significant 1.42 for those hired before 1950 and less than l for 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 an excess mortality from nonrespiratory 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 and complications of people with beryllium-related diseases, including both 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 through 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 among people who had acute beryllium pneumonitis (SMR, 2.32) than among 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 under 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 among 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 with an odds ratio (OR) of 1.5 (95% CI, 0.6-3.9). The authors concluded that their study did not support the hypothesis that occupational exposures to the chemicals they studied appreciably increased the risk of cancer of the central nervous system. IARC (1993) noted that there was an increasing risk of cancer of the central nervous system 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* in humans of the carcinogenicity of beryllium and beryllium compounds. That 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 exposures were 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 observed in the Beryllium Case Registry cohort.
- Increasing risks with increasing latency.

IARC pointed out the following limitations:

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

A series of letters and papers issued after the IARC report raised concerns and objections about 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 making alternative adjustments and comparisons to address those issues resulted in 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 cohort in the Ward et al. study in 1992. The lung-cancer cases numbered 142 on the basis of a followup of the cohort through 1992, each of which was age- and race-matched to five controls. In addition to assessment of beryllium exposures, the potential for confounding by smoking was evaluated. The cases had lower lifetime exposures to beryllium. However, when a 10-year lag and a 20- year lag were applied, the exposure metrics were higher for cases. Furthermore, significant positive trends with 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) suggested that concomitant exposure to acid mists and vapors was a possible confounder, noted difficulties with the adjustment for tobacco-smoking, and raised issues about the selection of control subjects. The study results were reanalyzed with different methods for summarizing exposure histories and for matching controls to cases (Levy et al. 2007). Each alternative method resulted in lower exposure ORs that were nonsignificant.

Brown et al. (2004) published a study of lung cancer and internal doses of plutonium among workers at the Rocky Flats plant in Colorado. The case-control study obtained information on smoking histories and on cumulative exposures to four lung carcinogens: asbestos, beryllium, hexavalent chromium, and nickel. In their analysis, none of the exposures to the four carcinogens was significantly associated with lung-cancer mortality.

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 4-2). Lung neoplasms have been found in rats and monkeys exposed to beryllium compounds via inhalation.

Albino Sherman and Wistar rats (male and female) were exposed via inhalation to an aqueous aerosol of beryllium sulfate tetrahydate (which contained beryllium at 35.7 $\mu g/m^3$) for 8 h/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 via inhalation to beryllium sulfate at 6 and 54.7 $\mu g/m^3$ for 6 h/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 $\mu g/m^3$ for 7 h/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 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, for 35 h/week (Reeves and Deitch 1969). The exposure durations were 800, 1,600, and 2,400 h. 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 (86%, 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 to 6 months, and anaplasia by 7 to 8 months.

Male and female rhesus monkeys (*Macaca mulatta*) were exposed to beryllium sulfate at 35 $\mu g/m^3$ for 6 h/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 4,070 h, 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 observed in a monkey that had been exposed for 3,241 h. 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 or 0.04 mg/m^3) or beryllium chloride (at 0.2 or 0.02 mg/m^3) for 1 h/day, 5 days/week, for 4 months

TABLE 4-2 Inhalation Carcinogenicity Studies of Beryllium

Reference	Species	Route	Dose	Findings
Acute Exposures				
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 was 325 d; 1 of 184 rats had lung tumors after 2 years
Groth et al. 1980	Rat	Intratracheal	Be at 0.5 or 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 and 9 of 16 treated with Be, 7 of 20 and 9 of 26 treated with Be-Cr, 1 of 21 and 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, or 18 mg/kg (low- and high-fired)	Malignant epithelial lung tumors found;. 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
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 Exposures				
Schepers et al. 1957	Rat	Inhalation	Be at 35.7 $\mu g/m^3$ as $BeSO_4$ (8 h/day, 5.5 days/week for up to 6 months)	Lung-cancer rates higher in exposed rats than in controls
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 in paper
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 Exposures				
Dutra et al. 1951	Rabbit	Inhalation	BeO at 1, 6, 30 µg/L (5 h/day, 5 days/week, for 9-13 months) Particle size: 0.285 µm (mean), 0.11-1.25 µm (range)	6 of 9 rabbits developed osteosarcomas after 1 year

TABLE 4-2 *Continued*

Reference	Species	Route	Dose	Findings
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 h/day, 5 days/week, for 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) describes 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 h/day, 5 days/week, for 72 weeks) Particle size: 0.118 µm	All rats developed lung tumors (adenocarcinomas) by 13 months
Vorwald 1968	Monkey	Inhalation	Be SO_4 at 35 µg/m^3 (6 h/day, 5 days/week, with various interruptions and variable durations up to 4,070 h)	8 of 12 monkeys had pulmonary anaplastic carcinomas (adenomatous and epidermoid patterns); first tumor observed after 3,241 h of exposure
Reeves and Deitch 1969	Rat	Inhalation	$BeSO_4$ at 35.16 µg/m^3 (35 h/week for 800, 1,600, 2,400 h) Particle size: 0.21 µm (mean)	19 of 22 young rats and 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, hamser, squirrel monkey	Inhalation	Bertrandite dust at 15 mg/m^3 (Be at 210 µg/m^3) or beryl ore at 15 mg/m^3 (Be at 620 µg/m^3) (6 h/day, 5 days/week, for 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, or epidermoid tumors); no increased incidence of tumors in rats from dust or in other species from either compound
Litvinov et al. 1975	Rats	Inhalation	BeF_2 at 0.04 or 0.4 mg/m^{3}or $BeCl_2$ at 0.02 or 0.2 mg/m^3 (1 h/day, 5 day/week, for 4 months)	Lung tumors found in treatment groups
Litvinov et al. 1984	Rats	Inhalation	BeO or $BeCl_2$ at 0.8, 4, 30, or 400 µg/m^3 (1 h/day, 5 days/week, for 4 months)	Malignant lung tumors found in 3 of 44, 4 of 39, 6 of 26, 8 of 21 in BeO group and in 1 of 44, 2 of 42, 8 of 24, 11 of 19 in $BeCl_2$ group, respectively

Continued on next page

TABLE 4-2 *Continued*

Reference	Species	Route	Dose	Findings
Finch et al. 1998b	Mouse ($p53^{+/-}$ knockout and $p53^{+/+}$ wild-type)	Inhalation	15 or 60 Be µg (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 found 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, 110, 40, 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 and cells 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 downregulation of genes involved in DNA synthesis, repair, recombination (such as *MCM4*, *MCM5*, *PMS2*, *Rad23*, DNA ligase I)
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 for kinases MEK1, ERK1, p38 MAPK, JNK; increases also seen in NF-κB, CREB transcription factors, c-*fos*, and c-*myc*

Note: 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.

(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 for 1 h/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 none was 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 for 6 h/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 means 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 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 were received a single, nose-only exposure to a beryllium metal aerosol at 500 mg/m^3 for 8 min, at 410 mg/m^3 for 30 min, at 830 mg/m^3 for 48 min, or at 980 mg/m^3 for 39 min (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.

SUMMARY

Genotoxicity studies of beryllium have yielded conflicting results that appear to be somewhat compound dependent. The committee will critically evaluate the literature in its next report and consider how the information should be factored into the carcinogenic assessment of beryllium.

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 the International Agency for Research on Cancer, the U.S. Environmental Protection Agency, and the National Toxicology Program. In its second report, the committee will focus on assessing the collective evidence in characterizing the carcinogenic potential of beryllium and estimating carcinogenic risks.

5

Assessment of Other Health End Points

As described in Chapter 1, this report addresses the committee's charge to provide an independent review of the toxicologic, epidemiologic, and other relevant data on beryllium, including carcinogenic and non-carcinogenic effects. The two principal health end points currently of concern in connection with inhaled beryllium, i.e., sensitization that leads to chronic beryllium disease (CBD) and cancer, were discussed in Chapters 3 and 4, respectively. 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 with CBD would be expected to occur only after exposure much greater than that at 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 were identified by EPA that could be used to derive an oral RfD.

This chapter completes the charge for the first report by examining 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 been conducted that examined the reproductive or developmental effects of beryllium at doses relevant to current occupational exposures?
- Have any studies been conducted that distinguish 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 examined in the following sections. Reproductive and developmental effects of beryllium are considered first and 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 studies but no inhalation studies. 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.

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 and fetal-mortality surveys. 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 for 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).

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 be a reason for 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 limited number of 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, 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 post 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 are 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 injecting beryllium salts 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.

OTHER EFFECTS

Extrapulmonary effects of beryllium compounds are not common and most often secondary to severe lung disease or related to extra-pulmonary granulomatous lesions in humans. Systemic effects of beryllium are generally observed only at high doses in animals. ATSDR (2002) provides a comprehensive review of both human and animal data. Cardiovascular effects in humans (cor pulmonale) and animals (heart enlargement or increased 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 in the liver, have not been reported in humans or animals. Kidney stones and increased calcium in blood and urine 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-gland effects have been reported in animals. Neurologic effects have not been noted in humans or animals after inhalation of beryllium.

SUMMARY

Studies of reproductive and development effects, as well as other extrapulmonary effects, have generally been observed only at doses higher than the lowest doses that induce CBD or cancer.

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Appendix

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 at 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 at 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, 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 at 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 at the New York University (NYU) School of Medicine. He is also director of the Inhalation Facility for the National Institute for Environmental Health Sciences Center of Excellence. His research interests are 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 an associate professor in the Department of Medicine at 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 the U.S. Environmental Protection Agency'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 at the Medical University of South Carolina. He also holds an appointment as clinical professor in the Department of Radiology at 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 at 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 at 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 at 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 formerly 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 for 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 at 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 at 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 the Center to Protect Workers' Rights, a research institute devoted to improving health and safety in the construction industry. Her research interests are in asbestos-related diseases and 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.