Potential Health Risks to DOD Firing-Range Personnel from Recurrent Lead Exposure

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Committee on Toxicology

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Preface

Lead poses an occupational health hazard, and the Occupational Safety and Health Administration (OSHA) developed a lead standard in 1978 for general industry that regulates many workplace exposures to this metal, including exposures on firing ranges. A large body of literature on health effects of lead exposure and factors that influence lead toxicity has been published since the lead standard was established. Most recently, the National Toxicology Program released a monograph on the health effects of low-level lead exposure, and the US Environmental Protection Agency is in the process of updating its Integrated Science Assessment for Lead in support of its review of the National Ambient Air Quality Criteria for lead.

In light of improved knowledge about the hazards posed by occupational lead exposure, the Department of Defense (DOD) asked the National Research Council to evaluate potential health risks related to recurrent lead exposure of firing-range personnel. Specifically, DOD asked the National Research Council to determine whether current exposure standards for lead on DOD firing ranges protect their workers adequately and to evaluate potential risk-assessment options.

In response to DOD's request, the National Research Council convened the Committee on Potential Health Risks from Recurrent Lead Exposure of DOD Firing Range Personnel, which prepared this report. The members of the committee were selected for their expertise in general toxicology, inhalation toxicology, neurotoxicology, reproductive and developmental toxicology, immunotoxicology, toxicokinetics, epidemiology, industrial hygiene, occupational medicine, exposure assessment, risk assessment, and biostatistics (see Appendix A for biographic information on the members).

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 manu-

script remain confidential to protect the integrity of the deliberative process. We thank the following for their review of this report: Floyd Bloom, The Scripps Research Institute; Deborah Cory-Slechta, University of Rochester; William Halperin, University of Medicine and Dentistry of New Jersey; David Lawrence, The Wadsworth Center; William J. Moorman, National Institute for Occupational Safety and Health (retired); Rosemary Sokas, Georgetown University; Kenneth Still, Portland State University; and Rochelle Tyl, RTI International.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by Robert Goyer, University of Western Ontario (retired), and Linda McCauley, Emory University. Appointed by the National Research Council, they were responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the 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; Keri Stoever, research assistant; Tamara Dawson, program associate; Norman Grossblatt, senior editor; and Mirsada Karalic-Loncarevic, manager of the Technical Information Center.

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

David C. Dorman, DVM, PhD, *Chair*
Committee on Potential Health Risks
from Recurrent Lead Exposure of DoD
Firing Range Personnel

Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
AIHA®	American Industrial Hygiene Association
ALA	aminolevulinic acid
ALAD	delta-aminolevulinic acid dehydratase
ALAU	aminolevulinic acid level in urine
AOEC	Association of Occupational and Environmental Clinics
AQCD	air quality criteria document
BAT	biological tolerance values (German)
BAEP	brainstem auditory evoked potential
BEI®	biological exposure index
BLL	blood lead level
$CaNa_2EDTA$	calcium disodium ethylenediamine tetraacetic acid
CBLI	cumulative blood lead index
CD	cluster of differentiation
CDC	Centers for Disease Control and Prevention
CES-D	Center for Epidemiological Studies – Depression Scale
CI	confidence interval
CKD	chronic kidney disease
CPA	Center for Policy Alternatives (at the Massachusetts Institute of Technology)
CPT	current perception threshold
CSTE	Council of State and Territorial Epidemiologists
CTL	cytotoxic T lymphocyte
CVD	cardiovascular disease
DBP	diastolic blood pressure
DMSA	2,3-dimercaptosuccinic acid
ECG	electrocardiogram
EEG	electroencephalogram
EPO	erythropoietin
FEP	free erythrocyte protoporphyrin

GFR	glomerular filtration rate
HFE	human hemochromatosis protein
HR	hazard ratio
HSE	Health and Safety Executive
Ig	immunoglobulin (also called an antibody)
IgA	immunoglobulin A
IgD	immunoglobulin D
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IFNγ	interferon gamma
IL-10	interleukin-10 cytokine (released from T_H-2 cells)
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MMSE	Mini-mental State Examination
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAG	*N*-acetyl-beta-D-glucosaminidase
NF-κB	nuclear factor κB
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute for Occupational Safety and Health
NK-CD56$^+$	natural killer cells
NTP	National Toxicology Program
NIEHS	National Institute of Environmental Health Sciences
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
PEL	permissible exposure limit
PKC	protein kinase C
PNS	peripheral nervous system
POMS	Profile of Mood State
ROS	reactive oxygen species
SBP	systolic blood pressure
SCOEL	Scientific Committee on Occupational Exposure Limits (European Union)
SD	standard deviation
SE	standard error
SMR	standardized mortality ratio
SRT	simple reaction time
SWHS	Swedish Women's Health Study
T_H	T-helper lymphocyte
T_H1	T-helper 1 lymphocyte
T_H2	T-helper 2 lymphocyte
TLV®	threshold limit value
TNF-α	tumor necrosis factor α (T_H-1 pro-inflammatory cytokine)

TWA	time-weighted average
VEP	visual evoked potential
WMC	white matter change
XRF	x-ray fluorescence
ZPP	zinc protoporphyrin

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Summary

Lead is a ubiquitous metal in the environment, and its adverse effects on human health are well documented. Lead interacts at multiple cellular sites and can alter protein function in part through binding to amino acid sulfhydryl and carboxyl groups on a wide variety of structural and functional proteins. In addition, lead mimics calcium and other divalent cations, and it induces the increased production of cytotoxic reactive oxygen species. Adverse effects associated with lead exposure can be observed in multiple body systems, including the nervous, cardiovascular, renal, hematologic, immunologic, and reproductive systems. Lead exposure is also known to induce adverse developmental effects in utero and in the developing neonate.

Lead poses an occupational health hazard, and the Occupational Safety and Health Administration (OSHA) developed a lead standard for general industry that regulates many workplace exposures to this metal. The standard was promulgated in 1978 and encompasses several approaches for reducing exposure to lead, including the establishment of a permissible exposure limit (PEL) of 50 $\mu g/m^3$ in air (an 8-hour time-weighted average [TWA]), exposure guidelines for instituting medical surveillance, guidelines for removal from and return to work, and other risk-management strategies. An action level of 30 $\mu g/m^3$ (an 8-hour TWA) for lead was established to trigger medical surveillance in employees exposed above that level for more than 30 days per year. Another provision is that any employee who has a blood lead level (BLL) of 60 µg/dL or higher or three consecutive BLLs averaging 50 µg/dL or higher must be removed from work involving lead exposure. An employee may resume work associated with lead exposure only after two BLLs are lower than 40 µg/dL. Thus, maintaining BLLs lower than 40 µg/dL was judged by OSHA to protect workers from adverse health effects. The OSHA standard also includes a recommendation that BLLs of workers who are planning a pregnancy be under 30 µg/dL.

A large body of literature on health effects of lead exposure and factors that influence lead toxicity has been published since the 1978 OSHA standard was established. Most recently, the US National Toxicology Program (NTP) released a monograph on the health effects of low-level lead exposure, defined by the NTP as BLLs of under 10 µg/dL and in some cases under 5 µg/dL. The

US Environmental Protection Agency (EPA) has also released an external review draft of its Integrated Science Assessment for Lead in support of its review of the National Ambient Air Quality Criteria for lead. The NTP and EPA reviews provide compelling evidence of a variety of health effects associated with BLLs of 10-40 μg/dL and of some health effects at lower levels.

In light of knowledge about the hazards posed by occupational lead exposure, the Department of Defense (DOD) asked the National Research Council to evaluate potential health risks from recurrent lead exposure of firing-range personnel. Specifically, DOD asked the National Research Council to determine whether current exposure standards for lead on DOD firing ranges protect its workers adequately. To address its charge, the committee focused on determining whether there is evidence of adverse health effects in people who have BLLs of 40 μg/dL or lower because that is the implicit level in the OSHA standard to protect workers from adverse health effects; indeed, the standard allows workers to have a BLL up to 40 μg/dL for a 40-year working lifetime. The committee also considered measures of cumulative lead dose. These can include the measurement of lead stored in bone or the calculation of a cumulative blood lead index (CBLI). At a BLL of 40 μg/dL, a CBLI of 1,600 μg-years/dL (the product of a BLL of 40 μg/dL and a 40-year working lifetime) could be achieved. The index is roughly equivalent to a bone (tibia) lead concentration of 40-80 μg/g (2.5-5% of the CBLI). Thus, the committee also sought evidence that would relate these cumulative measures of lead dose to adverse health effects.

The committee obtained data from the US military services to determine current lead exposure on DOD firing ranges. Data collected for the last 5 years show that the OSHA PEL for lead of 50 $\mu g/m^3$ was frequently exceeded on Army, Navy, and Air Force firing ranges, in some cases by several orders of magnitude. BLL data on firing-range personnel were not available from either the Army[1] or the Navy because the available measurements were not linked to job classifications, but the Air Force reported that BLLs of its firing-range personnel were all under 40 μg/dL.

A review of the epidemiologic and toxicologic data allowed the committee to conclude that there is overwhelming evidence that the OSHA standard provides inadequate protection for DOD firing-range personnel and for any other worker populations covered by the general industry standard. Specifically, the premise that maintaining BLLs under 40 μg/dL for a working lifetime will protect workers adequately is not valid; by inference, the OSHA PEL and action level are also inadequate for protecting firing-range workers. The committee found sufficient evidence to infer causal relationships between BLLs under 40 μg/dL and adverse neurologic, hematopoietic, renal, reproductive, and cardio-

[1]After the committee completed its evaluation and released the prepublication draft of this report, the Army submitted data on BLLs for Department of the Army civilian personnel working at shoot houses. The Army's submission can be obtained by contacting the National Research Council's Public Access Records Office at (202) 334-3543 or paro@nas.edu.

vascular effects. The committee also found compelling evidence of developmental effects in offspring exposed to lead in utero and during breastfeeding, and this raises additional concerns about exposures of women of childbearing age.

BLLs are generally considered to represent recent exposure to lead (on the basis of the lifespan of the erythrocyte and BLL's representing the integrated dose over the prior 4 months or so). Because lead in blood is in equilibrium with lead stored in bone, where lead can reside for decades, some BLLs can also reflect past higher or cumulative exposures. Therefore, BLLs measured later in life can reflect both current and past cumulative exposure, so interpretation is difficult. For example, studies that used data from the National Health and Nutrition Examination Survey to relate BLLs to risk of chronic kidney disease have reported a striking rise in risk of the disease in the highest quintile of BLL compared with the lowest quintile even though the mean BLL in the highest quintile is only 3-4 μg/dL. Those in the highest quintile may have had higher BLLs earlier in life that resulted in a greater cumulative lifetime exposure to lead than may be inferred from the current BLL, which is in equilibrium with possibly higher bone stores. In that case, cumulative exposure is more likely to be associated with the observed chronic effect on renal function, so the BLL of 3-4 μg/dL might not represent a "threshold level".

Despite those shortcomings of the BLL, the committee decided to present the range of BLLs that have been associated with various acute and chronic health outcomes:

- Adverse renal effects are manifested by increases in serum creatinine at BLLs of 8-12 μg/dL, decreases in creatinine clearance and glomerular filtration rate at BLLs of 20-30 μg/dL, and effects on renal endocrine functioning at BLLs of 30-40 μg/dL. The latter might be responsible, in part, for the increases in blood pressure observed with high BLLs.
- Adverse cardiovascular effects of concern include increased blood pressure at BLLs under 10 μg/dL and increased cardiovascular-disease mortality at BLLs of 8 μg/dL or higher. A relationship between BLLs under 40 μg/dL and cardiovascular mortality and some subclinical cardiovascular outcomes has also been observed in older and other susceptible subpopulations.
- Adverse nervous system effects include dose-related changes in cognitive and psychomotor performance at a BLL of about 18 μg/dL and such neurophysiologic changes as hearing loss at BLLs under 10 μg/dL, changes in balance at BLLs of about 14 μg/dL, changes in visual function at BLLs of 17-20 μg/dL, slowed auditory evoked potentials at BLLs of 26-30 μg/dL, changes in autonomic function at BLLs over 20 μg/dL, and changes in peripheral sensory nerve function at BLLs around 30 μg/dL.
- Adverse hematologic effects include impaired formation and impaired survival of erythrocytes at BLLs of about 20-30 μg/dL.
- Adverse developmental effects were found in infants and children at maternal BLLs under 10 μg/dL, and reduced fetal growth and low birth weight

were observed at maternal BLLs under 5 μg/dL. Low birth weight has been shown to have long-term effects on cognitive function and to increase susceptibility to some chronic illnesses later in life.

- The International Agency for Research on Cancer, the NTP, and EPA have identified lead as likely to be carcinogenic to humans largely on the basis of nonhuman experimental evidence. The committee found no reason to disagree with those conclusions but notes that the available human studies were insufficient to support a conclusion about an association of BLLs with cancer in humans.

Given the committee's findings about the inadequacy of the OSHA lead standard, DOD should review its guidelines and practices for protecting workers from lead exposure on firing ranges. One consideration should be a lowering of acceptable BLLs to more stringent levels that reduce the risk of adverse health effects. Professional organizations have called for more protective guidelines. For example, the American College of Occupational and Environmental Medicine has recommended medical removal of workers who have BLLs over 20 μg/dL, and the Council of State and Territorial Epidemiologists has suggested that the case definition of an elevated BLL in adults be changed from 25 μg/dL to 10 μg/dL. The Association of Occupational and Environmental Clinics has recommended more stringent guidelines for medical management of lead-exposed workers, which have been incorporated into DOD's guidance for occupational medical examinations and surveillance. All those organizations recommend that BLLs be kept under 5 μg/dL in pregnant women to reduce the risk of spontaneous abortion. The Centers for Disease Control and Prevention has developed guidelines that recommend followup activities and interventions beginning at a BLL of 5 μg/dL in pregnant women.

Because little BLL data on DOD range workers were available, it was not possible to determine potential health risks to this specific population. However, data on airborne concentrations of lead on DOD firing ranges indicate that the current OSHA PEL is exceeded in the performance of some job duties, in some cases by several orders of magnitude, and this may lead to increased BLLs. Thus, DOD should consider analyzing BLLs of a representative sample of range workers in all the services and comparing them with BLLs linked to adverse health outcomes to understand potential health risks and to guide risk-management decisions at its ranges. Protecting workers from exposure to lead involves an integrated approach that combines protective air and BLL guidelines, environmental and biologic monitoring to ensure that the guidelines are met, environmental controls to minimize exposure to lead, and appropriately designed medical surveillance. Consideration should be given to performing risk analyses of available control options to determine the best way to minimize exposure to lead. Such analyses could include assessment of exposure to lead (and other contaminants) at ranges where leadfree or jacketed ammunition is primarily used, assessment of risks related to range design and ventilation controls, and evaluation of the contribution of surface contamination to oral lead exposure.

The results of the analyses will help to inform decisions about setting new air exposure limits for lead on firing ranges, about whether to implement limits for surface contamination, and about how to design lead-surveillance programs for range personnel appropriately.

1

Introduction

Despite changes in military tactics and technology, proficiency in the handling of weapons remains a cornerstone in the training of the modern combat soldier. Modern military forces are trained on one or more small arms, including handguns, shotguns, rifles, and machine guns. Many of the projectiles used in military small arms contain lead. Exposure to lead during weapons training on firing ranges therefore is an important occupational-health concern.

Lead is a ubiquitous metal in the environment, and its adverse effects on human health are well documented. The nervous system is an important target of lead toxicity, which causes adverse cognitive, mood, and psychiatric effects in the central nervous system of adults; causes various peripheral nervous system effects; and has been linked to neurodegenerative diseases. Lead exposure also causes anemia, nephrotoxicity, a variety of adverse reproductive and developmental effects, small increases in blood pressure and an increased risk of hypertension particularly in middle-aged and older people, and various effects in other organ systems, including joint pain and gastrointestinal pain (ATSDR 2007; EPA 2012; NTP 2012).

Various occupations involve lead exposure, including those in lead-smelting, battery-manufacturing, welding, construction, demolition, and firing ranges. Occupational exposure is often the most important source of lead exposure of adults (Shannon 1998). Regulations and guidelines limiting occupational lead exposure have been established by the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH®), and other regulatory agencies. Features common to the guidelines include an airborne exposure limit that is used to monitor lead in the workplace and a recommended blood lead level (BLL) to prevent adverse health effects.

OSHA's lead standard for general industry was established in 1978 (29 CFR 1910.1025). It includes a permissible exposure limit (PEL) of 50 $\mu g/m^3$ (an 8-hour time-weighted average [TWA]) and an action level of 30 $\mu g/m^3$ (an 8-hour TWA). If an employee is exposed above the action level for more than 30

days per year, an employer is required to provide a medical surveillance program that includes blood-lead sampling and medical examinations. OSHA also requires that any employee who has a BLL of 60 µg/dL or higher or three consecutive BLLs averaging 50 µg/dL or higher be removed from work that involves lead exposure. The employee may resume work that entails lead exposure only after two BLLs are under 40 µg/dL. The OSHA standard assumes that a population of workers exposed at the PEL of 50 $\mu g/m^3$ will have an average BLL of 40 µg/dL or lower. It allows workers to have BLLs of up to 40 µg/dL for a working lifetime of 40 years. For workers who wish to plan pregnancies, OSHA recommends a BLL of under 30 µg/dL.

The NIOSH (1978) and ACGIH (2001a, b) guidelines are designed similarly to maintain BLLs below a threshold. NIOSH's recommended exposure limit of 50 $\mu g/m^3$ was established in 1978 and was aimed at maintaining the BLL below 60 µg/dL. ACGIH established a biological exposure index (BEI®) in 1995 of 30 µg/dL, and its threshold limit value (TLV®) of 50 $\mu g/m^3$ was intended to maintain workers' BLLs below the BEI.

Exposure standards and guidelines for protecting the general public from lead in ambient air, drinking water, soil, and consumer products have been established by such agencies as the US Environmental Protection Agency (EPA), the Agency for Toxic Substances and Disease Registry, the Centers for Disease Control and Prevention, the National Toxicology Program (NTP), and the US Food and Drug Administration. The standard for lead in air is undergoing review by EPA. Lead is one of several criteria pollutants for which EPA has established National Ambient Air Quality Standards (NAAQSs). In February 2012, EPA released an Integrated Science Assessment for Lead (Second External Review Draft), which indicates that the NAAQS for lead will probably be reduced (EPA 2012). In June 2012, the NTP completed an evaluation of the scientific evidence on the potential health effects of low-level lead exposure and concluded that "there is *sufficient* evidence that [BLLs] <10 µg/dL and <5 µg/dL are associated with adverse health effects in children and adults" (NTP 2012).

Because changes in environmental and occupational guidelines could affect the use of lead by the Department of Defense (DOD), the department asked the National Research Council to conduct a study of potential occupational health risks posed by exposure to lead. Of particular interest was lead exposure on small-arms firing ranges, especially exposure of range workers, who experience it recurrently. In response, the National Research Council convened the Committee on Potential Health Risks from Recurrent Lead Exposure of DOD Firing Range Personnel.

THE COMMITTEE'S TASK

Members of the committee were selected for their expertise in general toxicology, inhalation toxicology, neurotoxicology, reproductive and developmental toxicology, immunotoxicology, toxicokinetics, epidemiology, industrial

hygiene, occupational medicine, exposure assessment, risk assessment, and biostatistics. The committee was specifically asked to accomplish the following task:

> An expert committee will assess the potential health risks to Department of Defense firing range instructors and other personnel who experience recurring environmental exposures to lead at small-arms firing ranges. Information will be evaluated on recurrent lead exposures at such firing ranges, and relevant toxicological and epidemiological information on any carcinogenic and non-carcinogenic effects of exposures to lead will be evaluated. The evaluated information will include reviews by the Environmental Protection Agency and the National Toxicology Program. The committee will assess whether current exposure standards used at ranges are protective and will evaluate potential risk assessment options.

APPROACH TO THE STUDY

There is a large amount of scientific literature on lead. To manage the amount of data that it had to review and to structure its analysis to address its task in a timely manner, the committee established the following boundaries for its review:

- *Evaluation of health effects.* The committee did not conduct a systematic review of the lead literature or conduct a formal risk assessment, but it took advantage of the recent compilations of the toxicologic and epidemiologic studies of lead by the NTP, EPA, and the International Agency for Research on Cancer. Those reviews were used as a basis for identifying the primary health end points that would be of concern for firing-range personnel. The committee supplemented the reviews by evaluating relevant new studies related to those health effects and by determining what exposures would be of greatest concern. The following considerations were used to focus the committee's review further:

  - Human studies were the primary source of data, and animal studies and mechanistic information were used when appropriate. Few epidemiologic studies of firing-range personnel were found; therefore, occupational and other studies involving lead exposure were sought. Studies that considered potential covariates in their statistical analyses were favored.
  - Acute, chronic, and latent health effects of lead exposure were considered. Data on clinical disease outcomes were believed to be more relevant to the committee's charge than data on early biologic effects.
  - The preferred measures of exposure were the BLL as a measure of recent exposure and the cumulative blood lead index (CBLI) or bone lead concentrations as a measure of cumulative dose.
  - Health-effects data on BLLs under 40 µg/dL were considered primarily, because the current OSHA standard aims to maintain BLLs below

that. Evidence on health effects at corresponding estimates of CBLI of 1,600 µg-years/dL (40 years at 40 µg/dL) and tibia lead levels of 40-80 µg/g (2.5-5% of the CBLI) was also sought. The committee decided that if it found evidence to suggest that health effects occur below those BLLs, CBLIs, or bone lead values, it would have to conclude that the OSHA exposure standard is inadequate.

- *Population characteristics.* Firing-range workers may be active-duty military or civilians. The health of the population of firing-range workers is probably similar to that of the general working population. Special consideration was given to women who might be pregnant or nursing or might become pregnant, because of the well-known effects of lead on obstetric outcomes.
- *Characterization of exposure on firing ranges.* The committee focused its attention on airborne lead exposures that are most likely to occur on DOD firing ranges. Measurements and evaluations conducted at DOD ranges were used primarily and were supplemented with information on other types of firing ranges.

In addressing the statement of task, the committee focused on answering the following questions:

1. Are OSHA's guidelines for using BLLs adequate to protect DOD firing-range personnel?
2. Is the current OSHA PEL sufficiently protective of DOD firing-range personnel?
3. Is the current OSHA action level for medical surveillance appropriate?
4. Were data gaps identified in answering the above questions? Is research needed to fill those gaps?

FIRING-RANGE ENVIRONMENTS

Military firing ranges are specialized facilities designed for small-arms practice. Firearms can be fired inside a closed firing range or on an outdoor range. Both configurations have the potential for contamination with products of combustion (primer) or with a lead-based projectile (bullet). Depending on the weapon and the application, various specialized types of projectiles may be used. For example, jacketed bullets often consist of a soft lead core that is partially or fully encased in a shell of harder metal (such as copper). Jacketed bullets can minimize lead vaporization and particle generation. Other types of ammunition include fragmentation bullets and frangible bullets (projectiles that are designed to disintegrate on contact with a surface harder than the bullets themselves). The increasing use of full-jacketed bullets, alternative metal projectiles, and non-lead-containing primers should reduce airborne lead exposure during live-fire exercises.

Generation of Atmospheric Lead on Firing Ranges

The committee sought but did not find data on chemical speciation of airborne lead particles on firing ranges. The following discussion therefore is a general characterization of atmospheric lead on ranges and applies primarily to nonjacketed lead-based ammunition with lead-containing primers. As a shooter pulls the trigger, the firing pin causes the primer, which contains lead styphnate (an explosive compound), to initiate the combustion of the gunpowder in the cartridge (Valway et al. 1989). The propellant burns at temperatures up to 1,000°C and can generate pressures of up to 1,400 kg/cm^2 (20,000 lb/in^2 [psi]), which propel the bullet down the barrel and toward the target (NEHC 2002). At 1,000°C, lead is vaporized at the base of the bullet and is released at the muzzle, and probably at the chamber when the shell casing is ejected, as lead fume, possibly as lead oxide fume as the lead fume reacts with atmospheric oxygen. As the bullet passes through the barrel, the barrel's rifling may generate additional particles that are released at the muzzle. Misalignment as the bullet enters the chamber from the magazine or revolver cylinder may also generate particles (Anania and Seta 1975; Fischbein et al. 1979). Large lead particles settle out quickly and deposit on the floor and other surfaces (Jones 1999; NEHC 2002). The bullets will fragment on striking the target or backstop, and this contributes to the airborne particles (Anania and Seta 1975; Fischbein et al. 1979); this source will be close to the target or backstop. Lead dust can contaminate the shooter's hands, face, and clothing. Dermal or oral exposure can also occur during weapon cleaning or during handling of empty casings.

US Military Firing Ranges

Military firing ranges can be indoor or outdoor and may be restricted to particular weapons (such as pistols, rifles, grenade launchers, and machine guns). A firing range typically is overseen by supervisory personnel (such as a range master or a range safety officer) who are responsible for ensuring that all safety rules are followed. Modern firing ranges are designed to prevent injury and property damage caused by misdirected or accidental firing and ricochets. They are also designed to direct ricochets away from the firing line (DOE 2012). Various materials are commonly used for that purpose, including concrete, gravel-filled concrete-masonry units, sand, stone logs, and earth. Some surfaces (such as baffles, wing walls, and metal connectors) may be covered with plywood to prevent back splatter.

Indoor ranges typically have specially constructed back walls or bullet traps, roofs, and side walls. Outdoor ranges may have concrete tubes to prevent stray shots (such as 10-m machine gun ranges), may lack a backstop to allow rounds to travel to their maximum range, or may be designed as fully or partially contained ranges (combination of side walls, bullet trap, canopy baffle, and

overhead baffles). Proper firing-range ventilation systems push and pull smoke and lead particles away from the shooting line to reduce lead exposure. However, because of the high noise levels produced at firing ranges (over 140 dB), many ranges have an air-locked corridor for soundproofing with doors at opposite ends of the egress corridor; most indoor ranges therefore have more lead-dust contamination than outdoor ranges because of their semiclosed (air) environment. Lead exposure in indoor ranges occurs at the firing line (for example, from primer ignition and muzzle blast) and at the bullet trap from projectiles' striking of the trap (Jones 1999).

Outdoor facilities are often used for longer-distance shooting (up to 1,000 m) under ambient environmental conditions (US Department of the Army 2010). High retaining walls, earth mounds, sandbag barriers, or specially designed traps are used on outdoor ranges to prevent bullets or shots from ricocheting outside the bounds of the range.

Firing-range environments that resemble common combat scenarios (for example, urban combat in Middle East operations) are increasingly used in the training of US armed forces. Mock facilities can include "shoot houses", method-of-entry buildings, maritime counterterrorism facilities, partition ranges that can be reconfigured to rooms of different sizes, combat ranges, combat villages, vehicle ranges (for land and air vehicles), and other full-size mockups (such as mockups of aircraft, shipside, and oil rigs). One subclass of specialized range mimics urban terrain, for example, Military Operations on Urbanized Terrain (MOUT). Each range can pose different risks of lead exposure. For example, MOUT training increases the possible contribution from fragmentation of bullets that strike targets inasmuch as it involves moving through mock buildings and firing at targets as close as 5 m away, a much shorter distance than the 25 m or more used on static target ranges (Mancuso et al. 2008). Resuspension and later inhalation of settled lead dust is another source of exposure as shooters move down range after firing; this could be an important contributor to lead exposure in MOUT training as shooters move through hallways, down lanes, and past targets at which they recently fired. Resuspension of settled lead dust is a major source of exposure during range maintenance and cleaning.

DEPARTMENT OF DEFENSE FIRING-RANGE PERSONNEL

The committee asked DOD to provide information about the range personnel in each service, including the number of personnel working on firing ranges, demographics, eligibility requirements, typical workday, requirements for physicals, and whether there are special considerations for pregnant range personnel. Little information was provided on the number of DOD ranges or on the number or demographics of range personnel. Below is a summary of information provided to DOD by each service and information located by the committee through its own literature searches.

US Army

The US Army has about 95 live-fire shoot houses at active installations and about 14 more that belong to reserve units. No information on the number indoor or outdoor ranges was provided. Firing-range personnel may have the following job classifications: range manager, range operations specialist, range technician, training technician, small-arms range lead, and live-fire range operations specialist (personal communication, J. Seibert, Office of the Deputy Under Secretary of Defense for Installations and Environment, July 2, 2012).

Some Army firing ranges have adopted lead-exposure guidelines more stringent than OSHA's. For example, the John F. Kennedy Special Warfare Center and School in Fort Bragg, North Carolina, has adopted medical removal-guidelines that are consistent with the recommendations of the American College of Occupational and Environmental Medicine. Instructors are removed if they have a single BLL over 30 µg/dL or two consecutive BLLs over 20 µg/dL (personal communication, J. Seibert, July 2, 2012). Army policy for pregnant range personnel is to follow DOD's *Occupational Medical Examinations and Surveillance Manual* (DOD 2007). The guidance is to maintain pregnant women or women who may be pregnant at BLLs under 5 µg/dL.

US Air Force

Air Force security forces combat-arms personnel operate 193 small-arms ranges (personal communication, J. Seibert, May 21, 2012). The Air Force has about 1,220 authorized range personnel. Personnel with this specialty (Air Force specialty code P0X1B and special experience identifier 312) are trained in combat-arms operation, facility maintenance, firearms instruction, occupational safety and health, and related subjects (US Department of the Air Force 2010). Combat-arms personnel must meet minimum physical requirements specified in the *Air Force Enlisted Classification Directory* related to physical condition, mobility and strength of upper and lower extremities, hearing, vision, and psychiatric health. Range workers typically get physicals twice a year. Potential medical reasons for exclusion from range work include those specified by OSHA. Other medical conditions that could require exclusion are assessed case by case. Workers may also be excluded if they are unable to wear required respirators. Duration of work on ranges varies with the weapon and course of instruction, but range workers typically work 8-10 hours per day 5 days per week. The daily average of work during live firing is estimated to be about 2.5-3 hours (personal communication, J. Seibert, May 21, 2012).

Pregnant military workers are required to undergo an evaluation for recommended modification of work activities. The Air Force Combat Arms Program (U.S. Department of the Air Force 2009) requires the local medical treatment facility to provide medical assessment of and line-of-duty determination on pregnant women who are working in and around firing-range operations or weapons maintenance. Civilian workers may also elect to undergo evaluation

with an assessment in the interest of fetal health and the possibility of recommended modification of work activities. Modifications of work activities are site-specific and worker-specific (personal communication, J. Seibert, May 21, 2012).

US Navy and Marine Corps

No information on the number and types of ranges in the Navy or Marine Corps was provided. The Navy has small-arms marksmanship instructors (GM-0812), who conduct training in all phases of basic marksmanship. Duties include firearms safety, mechanical training on small arms, instructional and qualification firing, and basic range operations (US Department of the Navy 2011a). Firing-range personnel typically work 8 hours per day 5 days per week (personal communication, J. Seibert, May 2, 2012).

Firing-range occupational specialties in the Marine Corps include range officers (MOS 0930), marksmanship instructors (MOS 0931), small-arms weapons instructors (MOS 0932), and marksmanship coaches (MOS 0933). Range officers supervise marksmanship-training programs and develop marksmanship training doctrine and techniques. Duties may include planning range layout, organizing courses of instruction, interpretation and enforcement of regulation, inspecting weapons and ammunition, and supervising test firing of weapons. Marksmanship instructors teach in all phases of the Marine Corps marksmanship program on qualification and requalification on small-arms use, and small-arms weapons instructors conduct and supervise all small-arms marksmanship training. Marksmanship coaches analyze the performance of shooters during dry- and live-fire exercises for qualification and requalification. Weapons instructors and marksmanship coaches also assist in the operation of firing ranges (US Department of the Navy 2008).

Workers who may be exposed at or above the OSHA action level of 30 $\mu g/m^3$ for 30 days per year are included in the surveillance program. Medical examinations are conducted annually for each person who is found to have a BLL of 30 µg/dL or higher (NMCPHC 2011; US Department of the Navy 2011b). Clinicians may counsel workers who want to plan pregnancies to achieve BLLs lower than those specified by OSHA (30 µg/dL). Navy guidance indicates that it may be advisable for BLLs to be under 20 µg/dL preceding conception and during pregnancy. Women who have BLLs over 20 µg/dL might be advised to avoid uncontrolled lead exposure for 1-2 years before attempting to conceive (NMCPHC 2010).

LEAD EXPOSURE ON DEPARTMENT OF DEFENSE FIRING RANGES

DOD was asked to provide the committee with air-sampling data on lead and BLLs collected over the last 5 years for range personnel, if possible according to job classification. In response to the request, the US Army submitted data extracted from the *Defense Occupational and Environmental Health Readiness*

System—Industrial Hygiene (personal communication, J. Seibert, July 2, 2012). Information was available on only a few small-arms firing ranges. Table 1-1 shows that mean airborne concentrations of lead ranged from 0.7 to 238 $\mu g/m^3$ and that the current OSHA PEL of 50 $\mu g/m^3$ was exceeded to some degree in almost all duties. The greatest percentage of samples that were above the PEL were collected during weapons handling at shoot houses (60%) and during range maintenance and cleaning activities (50%). The Army's industrial-hygiene program offices use the concept of similar exposure groups. A person who has a given job classification may perform many duties, and a sample and its TWA may have been determined to be valid for many processes that a worker has been performing during the time when the sample was taken. Data provided by the Army show overlap in job duties, so it was difficult to distinguish which tasks might have accounted for the highest exposures. For example, a maximum airborne concentration of 4,386 $\mu g/m^3$ was reported for several duties in the categories of supervision, cleaning and maintenance, weapons handling and firing, fire services, and ambulance drivers. The available BLL data from 2007-2011 obtained from the Army's Occupational Health Program Surveillance Reports indicated that the percentage of screened employees who had "abnormal" results ranged from less than 1% to 5%. However, the reports did not identify the sources of lead exposure—for example, shoot houses, indoor ranges, or other occupationally related exposures, such as exposure to plumbing, pipefitting, or handling of cable sheaths—or indicate the magnitude of the abnormalities.

The Navy provided the committee with results of personal air monitoring at its firing ranges (personal communication, J. Seibert, May 2, 2012). Personal air breathing-zone monitoring was performed during the period January 2008-April 2012 for a variety of firing-range tasks (Table 1-2). Air samples were collected in accordance with the US Navy's standard operating procedures (US Navy *Industrial Hygiene Field Operations Manual*) (NEHC 2012). In general, nearly full-shift samples (for example, 7 hours of an 8-hour work shift or 11 hours of a 12-hour work shift) are used to evaluate TWA exposures. Sampling during the period of greatest exposure during an operation is also stressed. Data presented in Table 1-2 confirm that air lead concentrations can vary widely between job categories and the type of firing range. Concentrations were highest in the cleaning of ranges; 58% of the samples were above the PEL, and the mean concentration was 190 $\mu g/m^3$. Air measurements in other job categories were also well above the current OSHA PEL of 50 $\mu g/m^3$ (see Table 1-2). BLLs of firing-range personnel during that time were unavailable to the committee because the central Navy electronic medical-records data system does not include information about personnel by job classification.

The Air Force also provided the committee with air-monitoring data from 2007-2012 and was the only service[1] to provide data on BLLs of range instructors

[1]After the committee completed its evaluation and released the prepublication draft of this report, the Army submitted data on BLLs for Department of the Army civilian personnel working at shoot houses. The Army's submission can be obtained by contacting

(Table 1-3). With the exception of data from 2011, it can be seen that mean air lead concentrations over the 6-year sampling time were well above the current OSHA PEL of 50 μg/m^3. It can also be seen that individual ranges can have appreciably higher air lead concentrations that are several orders of magnitude higher than the PEL (maximum values ranged from 247 to 386,000 μg/m^3). The Air Force began substituting lead-free ammunition for small-arms training in 2004 (AFIOH 2008), but no distinction was made about whether the data in Table 1-3 included measurements taken on ranges where the substitution was implemented. The maximum BLLs of Air Force range instructors in 2008-2012 were below the current OSHA standard of 40 μg/dL.

In addition to the data provided by DOD, the committee reviewed published data on BLLs and air concentrations of lead reported in connection with civilian and military firing ranges (IARC 2006). Table 1-4 shows the large variability in air lead concentrations and BLLs measured within and between firing ranges. No clear relationship between air lead concentrations and BLLs is apparent; the table has examples of higher mean BLLs at firing ranges that have lower mean air lead concentrations and examples of lower BLLs at ranges that have higher mean air lead concentrations. The latter observation was particularly relevant to the committee's work because it suggests that there are limitations on the use of air lead monitoring to protect personnel in this setting, especially at lower air lead concentrations. Differences in air lead concentrations and BLLs on firing ranges may reflect differences in the use of personal protective equipment; range hygiene and ventilation; personal hygiene; hand-to-mouth behaviors; smoking, eating, and drinking policies and practices; and policies and practices concerning hand-washing and clothes-laundering.

ORGANIZATION OF THE REPORT

The committee organized its review into three major components: understanding the basis of occupational standards and guidelines for lead, exposure considerations for lead on DOD firing ranges, and health effects of lead exposure. Chapter 2 provides an overview of different occupational standards and guidelines for lead and their bases. In addition to US guidelines, the guidelines of relevant organizations of other countries are considered. Chapter 3 presents exposure considerations for lead, including an overview of routes of exposure, biomarkers, toxicokinetics and toxicodynamics, and exposure factors that influence health outcomes. Health effects of exposure to lead are discussed in Chapter 4 (noncancer effects) and Chapter 5 (cancer effects), with a focus on studies relevant to DOD firing-range personnel. Chapter 6 presents a summary of the committee's findings.

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the National Research Council's Public Access Records Office at (202) 334-3543 or paro@nas.edu.

TABLE 1-1 Airborne Lead Concentration During Performance of Different Job Duties on US Army Weapons and Small-Arms Firing Ranges[a]

Duty	No. Sites	No. Samples	Mean (μg/m^3)	Geometric Mean (μg/m^3)	Geometric Standard Deviation (μg/m^3)	Samples Above the PEL
Supervision						
Firing-range supervision, protective services	3	84	103	7	6,730	13.1%
Range supervision, monitor	1	58	239	11.2	6,340	6.9%
Range supervision	1	29	239	11.2	6,440	6.9%
Range support, range instructor	1	29	239	11.2	6.440	6.9%
Weapons or small arms, range supervision	5	106	74	12.3	4,580	11.3%
Cleaning and Maintenance						
Range, equipment repair, preventive maintenance, NOC[b]	1	5	0.7	0.7	1,150	0%
Range maintenance, cleaning, other	1	2	89.4	76.7	2,230	50%
Firing-range cleaning, protective services	3	39	26.6	8.1	5,570	17.9%
Range cleaning, scraping	1	2	89.4	76.7	2,230	50%
Firing-range pit cleaning, protective services	1	11	35.9	3.1	8,050	9.1%

Range or ground maintenance, heavy-equipment operator	1	29	239	11.2	6,440	6.9%
Range or ground maintenance	2	44	191	16.3	6,900	25%
Maintenance-structures ranges, multiple operations	4	6	0.8	0.4	3,510	0%
Range cleaning	1	22	24.3	13.3	3,710	27.3%
Weapons or small arms, backstop or pit cleanup	1	4	114	14.4	25,420	50%
Weapons or small arms, range cleaning	6	116	85.2	10.2	5,830	13.8%
Disposition of range residue, HM/HW hand cleanup	1	22	24.3	13.3	3,710	27.3%
Weapons Handling or Firing						
Firing range, testing NOC[b]	1	22	24.3	13.3	3,710	27.3%
Indoor range, small-arms firing	6	100	30.6	2.9	9,570	19%
Indoor firing range, ordnance testing	1	22	24.3	13.3	3,710	27.3%
Outdoors, weapons or small-arms firing	7	114	84.8	4.8	9,390	16.7%
Shoot house, weapons or small-arms firing, NOC[b]	1	15	97.7	33.8	6,750	60%
Shoot house, small-arms handling	3	48	37.2	2.4	12,030	20.8%

(Continued)

TABLE 1-1 Continued

Duty	No. Sites	No. Samples	Mean (μg/m^3)	Geometric Mean (μg/m^3)	Geometric Standard Deviation (μg/m^3)	Samples Above the PEL
Operations or Services						
Range operations, weapons and ordnance	1	4	114	14.4	25,420	50%
Skeet and trap range, recreational services	1	4	1.9	0.5	6,760	0%
Fire services, ranges	1	29	239	11.2	6,440	6.9%
Other						
Ambulance drivers or EMT, range	1	29	239	11.2	6,440	6.9%

[a]Data extracted from the Defense Occupational and Environmental Health Readiness System—Industrial Hygiene. Army industrial hygiene program offices use the concept of similar exposure groups. A person who has a given job classification may perform many duties. A sample and its TWA may have been determined to be valid for many processes that a worker may have been performing during the time when the sample was taken.
[b]Not otherwise classified.
Source: Personal communication, J. Seibert, Office of the Deputy Under Secretary of Defense for Installations and Environment, July 2, 2012.

TABLE 1-2 Airborne Lead Concentration During Performance of Different Job Duties on US Navy Weapons and Small-arms Firing Ranges

	Range Cleaning	Ammunition Handling	NOC[a]	Outdoor Range Firing	Indoor Range Firing	Range Supervision	Backstop Pit Cleanup	Breeching	Lead Indoor Simulated Marksmanship Trainer	Weapons and Ordnance NOC[a]
No. samples	19	3	138	9	50	106	19	14	11	4
Maximum, $\mu g/m^3$	848	78.4	482	558	442	342	29.6	18.7	40.6	0.92
Minimum, $\mu g/m^3$	2.12	25.5	0.46	4	0.71	0.71	0.71	3.5	0.8	0.71
Mean, $\mu g/m^3$	190	44	48	22	46	23	9	9	13	1
Geometric mean, $\mu g/m^3$	50	39	13	15	11	8	5	7	8	1
Geometric standard deviation, $\mu g/m^3$	8,169	1,849	5,980	2,669	4,730	4,274	3,669	1,940	3,476	1,140
Samples above PEL, %	58	33	31.9	22.2	16	14.2	0	0	0	0
95th percentile[b], $\mu g/m^3$	1,583	1,060	2,400	76	148	83	39	21	61	1

[a]Not otherwise classified. Not a specific operation that can be further classified.
[b]Lognormal distribution.
Source: Personal communication, J. Seibert, Office of the Deputy Under Secretary of Defense for Installations and Environment, May 2, 2012.

TABLE 1-3 Lead Exposure on US Air Force Firing Ranges (2007-2012)—Air Lead Concentrations on Weapons and Small-Arms Firing Ranges and Blood Lead Levels of Combat-Arms Training and Maintenance Instructors

	2007	2008	2009	2010	2011	2012
Air Sampling Data						
No. samples	81	139	307	154	303	100
No. locations	12	18	23	24	27	16
Maximum, µg/m^3	386,000	1,650	14,900	7,820	247	19,500
Minimum, µg/m^3	0.21	ND	0.03	ND	ND	ND
Mean (± SD) , µg/m^3	9,120 ± 51,081	82.3 ± 209	80.3 ± 850	82.8 ± 652	19.7 ± 31	267 ± 218
Blood Lead Levels						
No. samples	—	37	41	57	93	69
Maximum, µg/dL	—	31	16	23	26	21
Minimum, µg/dL	—	1	1	1	1	1
Mean (± SD) , µg/dL	—	5.0 ± 5.7	4.6 ± 4.0	4.1 ± 4.4	5.4 ± 4.6	5.2 ± 4.4

Abbreviations: ND, not detected; SD, standard deviation.
Source: Personal communication, J. Seibert, Office of the Deputy Under Secretary of Defense for Installations and Environment, May 21, 2012.

TABLE 1-4 Air and Blood Lead Concentrations Measured on Indoor and Outdoor Firing Ranges

			Blood Lead (µg/dL)		Lead in Air (µg/m^3)		
Country	Settings or Tasks	Job History (years)	Mean	Range	Mean	Range	Reference
China (Province of Taiwan)	Employees in indoor range	4-21	37.2	22.4-59.6	GA: 134 PBZ: 413	NR	Chau et al. 1995
New Zealand	Indoor small-bore rifle range	Recreational shooters	End of season: 55.0; start of season 33.3		GA: 140-210 PBZ: 120		George et al. 1993
Sweden	Indoor range						Svensson et al. 1992
	Powder gun	10.2	13.8[a]	6.9-22.8	660	112-2,238	
	Air gun	13.7	8.4[a]	2.0-22.2	4.6	1.8-7.2	
	On-duty and off-duty police officers	NR	5.0	1.0-18.2	NR		Löfstedt et al. 1999
		>9	3.7				
United Kingdom	Indoor range for police officers	NR	30-59		30-160		Smith 1976
	Soldiers	4.2	19.25	9.6-30.1	TWA: 190		Brown 1983
United States	Indoor range						
	Full-time employee	NR	30-77		Showroom: 2.7 Firing line: 13.6 Midway to target: 57.4 Target: 90.5		Novotny et al. 1987
	Part-time employee	NR	17-49				

(Continued)

TABLE 1-4 Continued

Country	Settings or Tasks	Job History (years)	Blood Lead (µg/dL) Mean	Blood Lead (µg/dL) Range	Lead in Air (µg/m^3) Mean	Lead in Air (µg/m^3) Range	Reference
	Covered outdoor range	NR	5.6 (pre-exposure) 10.7 (day 2) 14.9 (day 5) 8.7 (day 69)		GA: 68.4 PBZ: 128.5	3.8-298.6 34.7-314.3	Tripathi et al. 1989
	Indoor range with training February 3-April 28	Trainees					Valway et al. 1989
			6.45	<5-23.1	1,483-1,860	304-2,688	
			51.4	31.2-73.3	2,906-3,226	994-5,589	
			44.6	27.1-62.3	1,231	553-2,567[b]	
			39.8	23.1-51.2			
	Lead bullet				1,410		
	Nylon-coated				78.3		
	Copper-jacketed				43.1		
	Covered outdoor range using copper-jacketed bullets	NR	Before shooting: 6.0 ± 1.7 After shooting: 6.5 ± 1.5		GA: 9.53 PBZ: 5.88	5.50-14.56 0.42-7.66	Tripathi et al. 1990
	Uncovered outdoor range						Goldberg et al. 1991
		NR	28-66		—		
		NR	—		460-510 (3-h TWA)		
		NR	25-70		—		

	NR	—		100-170 (3-h TWA)		
		28-38		—		
Covered outdoor range						Tripathi et al. 1991
Nonjacketed bullets	Instructors	14.2-24.2[c]	10-27	67.1-211.1	36.7-431.5	
Jacketed bullets	Instructors		13.1-22.1		5.4-8.7	
University rifle range	Recreational shooters					Prince and Horstman 1993
Old ventilation		11.8-16.4	5-21	176	24-239	
New ventilation		13.2-13.6	8-23	129	67-211	

[a]Median value.
[b]New ventilation system installed.
[c]Range on three sampling dates.
Abbreviations: GA, general area; NA, not applicable; NR, not reported; PBZ, personal breathing zone; TWA, time-weighted average.
Source: Adapted from IARC 2006.

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2

Occupational Standards and Guidelines for Lead

This chapter describes occupational exposure guidelines for lead. The US standards and guidelines of the Occupational Safety and Health Administration (OSHA), the National Institute for Occupational Safety and Health (NIOSH), and the American Conference of Governmental Industrial Hygienists (ACGIH®) are presented first and then guidelines of other countries, including those of the European Union, Germany, and the United Kingdom. Features common to the guidelines include an airborne exposure limit as an 8-hour time-weighted average (TWA) and a recommended blood lead level (BLL) to prevent adverse health effects. Table 2-1 presents a comparison of the various occupational-exposure guidelines.

US STANDARDS AND GUIDELINES

Occupational Safety and Health Administration Lead Standard

OSHA was created in 1970 on passage of the Occupational Safety and Health Act (OSHAct), Public Law 91-596. The OSHAct became effective on April 28, 1971, and authorized the federal government to establish and enforce standards for occupational safety and health. The intention of the OSHAct was to ensure that all employees in the United States had safe working conditions. The OSHAct also required the head of each federal agency (except the US Post Office) to establish an occupational safety and health program that is consistent with the standards promulgated under the act.

The OSHA lead standard for general industry (29 CFR 1910.1025) was promulgated on November 14, 1978. It applied to all occupational exposures to lead *except* those associated with construction or agricultural work. The key components of the lead standard were the setting of a permissible exposure limit (PEL) of 50 $\mu g/m^3$ as an 8-hour TWA and the institution of a medical surveillance program for all employees who are or may be exposed above the 8-hour TWA action level (30 $\mu g/m^3$) for more than 30 days per year.

TABLE 2-1 Occupational-Exposure Guidelines for Lead

Agency	Air-Exposure Guideline (8-h time-weighted average)	Recommended Limit for Blood Lead Level	Year Approved
Occupational Safety and Health Administration	50 µg/m^3	40 µg/dL	1978
National Institute for Occupational Safety and Health	50 µg/m^3	60 µg/dL	1978
American Conference of Governmental Industrial Hygienists	50 µg/m^3	30 µg/dL	1987 (air) 1995 (blood)
European Council Directive 98/24	150 µg/m^3	70 µg/dL	1998
European Union Scientific Committee on Occupational Exposure Limits	100 µg/m^3	30 µg/dL	2002
German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area	None, because probably carcinogenic in humans	40 µg/dL for men and women over 45 years old 10 µg/dL for women under 45 years old	2006
United Kingdom Health and Safety Executive	150 µg/m^3	25 µg/dL for women of reproductive age 40 µg/dL for people 16-17 years old 50 µg/dL for all other employees	2002

Historical Context

In the years preceding the promulgation of the OSHA lead standard, airborne lead exposure limits of 150-200 µg/m^3 and BLLs of 80 µg/dL were followed (43 Fed. Reg. 52952 [1978]). Data that emerged in the middle 1970s suggested that those levels were too high and should be reduced.

OSHA provided the following rationale for the final standard (40 Fed. Reg. 52952 [1978]):

Health Effects: OSHA relied on studies that reported adverse health effects in conjunction with BLLs and considered both effects from acute exposure and, to the extent that they were known, effects of long-term lead exposure. In

addressing the array of adverse health effects, OSHA cited five stages of a disease process—"normal, physiological change of uncertain significance, pathophysiological change, overt symptoms (morbidity), and mortality" (p. 52594) and recognized that there was not a sharp distinction between stages but rather that they are on a continuum. OSHA went on to state that an adopted standard "must prevent pathophysiological changes from exposure to lead". In questioning whether both "clinical and subclinical effects" of exposure should be considered, OSHA judged that those terms represented "vast over-simplifications of a disease process and, therefore . . . avoided their use in the final standard" (p. 52963). OSHA regarded subclinical effects to be the "early to middle stages in a continuum of disease development process" (p. 52963).

OSHA summarized key studies on heme-synthesis inhibition (inhibition of the enzymes delta-aminolevulinic acid dehydrogenase [ALAD] and ferrochelatase) and anemia; on neurologic effects (central nervous system symptoms, behavioral symptoms, peripheral nerve effects, and results of nerve-conduction testing); on renal effects; and on reproductive effects. Except for reproductive effects, the evidence demonstrated adverse pathophysiologic effects at BLLs over 40 μg/dL; thus, 40 μg/dL was considered the upper acceptable limit. Concerning reproductive effects and effects on children (hyperactivity at BLLs as low as 25 μg/dL), "OSHA concludes that in order to protect the fetus and newborn from the effects of lead on the nervous system, blood lead levels must be kept below 30 μg/100 g [30 μg/dL]" for workers who wish to plan pregnancies (40 Fed. Reg. 52960 [1978]). OSHA also acknowledged at the time that for many of the adverse health effects there was evidence of a dose-response relationship but that the "no-effect level" remained to be determined.

Air-Blood Relationships: Although industry representatives maintained that BLLs could not be correlated with or predicted from air lead concentration, OSHA judged that despite some data limitations the collective data could be used to make estimates. OSHA described some studies that provided linear models and regression analyses. It relied predominantly on a physiologic model originally developed by S. R. Bernard and adapted by the Center for Policy Alternatives (CPA) that "combines experimentally observed properties of mammalian lead transport and metabolism, including consideration of the dynamics of blood lead response to long term exposure" (40 Fed. Reg. 52961 [1978]). The model also accounted for "the observed physical properties of airborne particulates encountered in the workplace, in order to produce a complete and accurate picture of the response of blood lead levels to particulates" (40 Fed. Reg. 52967 [1978]), and CPA included specific consideration of individual variability in response to air lead. The model was applied to exposures at air concentrations of 50, 100, and 200 $\mu g/m^3$, and the results were used to predict the percentage of workers that would fall within different BLLs. The results demonstrated the benefit of setting an air concentration of 50 $\mu g/m^3$ to reduce the number of workers who had predicted BLLs over 40 μg/dL. (See Chapter 3 for the committee's evaluation of the model and its assumptions.)

Approach to the Rule: OSHA's reasons for placing primary reliance on an air PEL for compliance and citations rather than on biologic monitoring included these: evaluation of the industrial environment focused on the direct measurement and control of sources of lead exposure whereas biologic monitoring was designed to ascertain problems of individual workers and was an indirect measure, or check, of the control of lead; biologic monitoring was not feasible for compliance and citation purposes; and biologic monitoring alone might not provide adequate protection for workers, because excessive exposure to lead would not result immediately in excessive BLLs.

Permissible Exposure Limit

The lead standard requires employers to ensure that no employee is exposed above the PEL. In 1971, OSHA set the initial PEL for lead at 200 $\mu g/m^3$ as an 8-hour TWA. The PEL was based on American National Standards Institute consensus standard z37.11-1969. The consensus standard did not provide any justification for its level of 200 $\mu g/m^3$ (43 Fed. Reg. 52952 [1978]). OSHA also used the ACGIH threshold limit value (TLV®) as a national consensus standard to establish the initial PEL (Public Law 91-596). The 1968 TLV for lead was also 200 $\mu g/m^3$ (43 Fed. Reg. 52952 [1978]). OSHA was required in the OSHAct to set standards by using national consensus standards within 2 years of the OSHAct's becoming effective (Public Law 91-596).

In 1973, NIOSH recommended that the PEL be lowered to 150 $\mu g/m^3$. On October 3, 1975, OSHA proposed a new PEL of 100 $\mu g/m^3$. After the proposal was made, OSHA requested comments, data, and opinions on the lower PEL. Hearings were held in multiple locations in 1977. In light of the information received during the comment period and the hearings, a new lead standard received final certification on August 8, 1978 (43 Fed. Reg. 52952 [1978]).

The OSHA lead standard set the PEL at 50 $\mu g/m^3$ as an 8-hour TWA, which was technically feasible for industry. In OSHA's opinion, a lower air lead concentration of 40 $\mu g/m^3$ would not offer a substantial benefit compared with 50 $\mu g/m^3$.

Action Level

An action level is an air concentration that triggers the initiation of required activities, such as exposure monitoring and medical surveillance. OSHA defined the action level for lead as "employee exposure, without regard to the use of respirators, to an airborne concentration of lead of 30 $\mu g/m^3$ averaged over an 8-hour period" (29 CFR 1910.1025(b)). Exposure monitoring is performed to determine whether employees are exposed to lead above the action level. Some requirements are instituted when the action level is exceeded (see the section "Medical Monitoring" below).

Exposure Monitoring

The lead standard requires that employers monitor their employees to determine their personal exposure to airborne lead. The monitoring must be done for the full work shift of at least 7 continuous hours. It must be done for every shift in which employees were exposed to lead and an evaluation of the data must assume that employees were not wearing respirators. When personal exposures are below the action level (30 $\mu g/m^3$), the result must be documented in writing, and no additional monitoring is required. When personal exposures exceed the action level but are below the PEL, additional personal monitoring is required every 6 months until two consecutive measurements, collected at least 7 days apart, are below the action level. For personal monitoring results above the PEL, additional monitoring must be done quarterly. The sampling frequency can be reduced to every 6 months only when two consecutive measurements, collected at least 7 days apart, are below the PEL (29 CFR 1910.1025(d)).

Engineering and Work-Practice Controls

Engineering and work-practice controls must be implemented whenever employees are exposed above the PEL for more than 30 days per year. The controls include the requirement for a written compliance program to reduce personal exposures to below the PEL. If engineering and work-practice controls do not reduce exposures to below the PEL, respirators must be worn. If mechanical ventilation is used to control exposures, the ventilation system must be evaluated quarterly for its effectiveness in controlling exposures (29 CFR 1910.1025(e)).

Respirator Protection and Personal Protective Equipment

When respirators are required, a respiratory-protection program must be implemented in accordance with 29 CFR 1910.134. The respirators can be half-mask, full-facepiece, or powered air-purifying respirators. High-efficiency particulate air-equivalent (HEPA-equivalent) filters are required (29 CFR 1910.1025(f)).

Personal protective equipment must be provided at no cost to employees when exposures exceed the PEL. The equipment may include face shields, vented goggles, and disposable shoe coverlets. The employer is responsible for cleaning or disposing of the equipment (29 CFR 1910.1025(g)).

Housekeeping and Hygiene Facilities and Practices

All surfaces must be kept as free as practicable of any accumulations of lead. Surfaces cannot be cleaned by using compressed air; vacuuming is the preferred method of cleaning. When vacuuming is shown not to be effective, shoveling or dry or wet sweeping may be used (29 CFR 1910.1025(h)).

When exposures exceed the PEL, an employer must provide dedicated changing rooms, a lunchroom under positive pressure, and shower facilities. Food, beverages, and tobacco products cannot be present, consumed, or used, and cosmetics cannot be applied anywhere in the facility, except in the changing room, lunchroom, or shower areas. Changing rooms must separate street clothes from contaminated work clothing in a way that prevents cross-contamination. Employees are not permitted to enter the lunchroom without removing lead from their protective work clothing. Employees must wash their hands and face before eating, drinking, smoking, or applying cosmetics, and they must shower at the end of each work shift (29 CFR 1910.1025(i)).

Medical Monitoring

The following are the key points of the OSHA lead standard for general industry regarding medical surveillance (29 CFR 1910.1025(j)):

- The employer institutes a medical surveillance program for all employees who are or may be exposed at or above the air action level of 30 $\mu g/m^3$.
- Monitoring is performed by or under the supervision of a licensed physician.
- A full medical examination and consultation shall be made available to an employee
    - Before the first assignment to an area that has lead at or above the action level.
    - At least once a year for an employee who had a BLL of 40 µg/dL or over at any time during the preceding 12 months.
    - As soon as possible on notification by an employee that he or she has developed signs or symptoms of lead intoxication, desires medical advice concerning the effects of lead (past or current) and the ability to procreate a healthy child, or who has difficulty in breathing during respirator fit test or use.
- A full medical examination will include
    - A detailed work and medical history.
    - A thorough physical examination.
    - Measurement of blood pressure.
    - Analysis of BLL, hemoglobin and hematocrit, erythrocyte indexes, peripheral smear morphology, zinc protophorphyrin (ZPP), blood urea nitrogen and creatinine, urinalysis with microscopic examination, and any other tests that a physician thinks are appropriate, including a pregnancy test or laboratory evaluation of male fertility if requested by the employee.
- Biologic monitoring (for all employees who are working at or above the action level) and medical removal protection:
    - BLL and ZPP levels evaluated every 6 months.

  - BLL and ZPP levels evaluated at least once every 2 months for each employee whose last BLL was 40 µg/dL or higher until two consecutive BLLs are under 40 µg/dL.
  - Removal from work of an employee who has a BLL of 60 µg/dL or higher or who has an average BLL of the last three tests (or the average of all BLLs over the preceding 6 months) of 50 µg/dL or higher.
  - Evaluation of BLL and ZPP levels *monthly* during medical-removal period.
  - Removal not needed when the last BLL was under 40 µg/dL.
  - Temporary removal of an employee who is working at or above the action level and has a medical condition that makes the employee more susceptible to the risk posed by lead.
- Medical-removal protection benefits include
  - Up to 18 months of medical-removal-protection benefits on each occasion when an employee is removed.
  - Employer's maintenance of earnings, seniority, and other employment rights as though the employee has not been removed.

Employee Information and Training

Employee training is required whenever there is a potential for exposure to airborne lead. Training must include the information provided in Appendixes A and B of 29 CFR 1910.1025. When employees are exposed above the action level, they must be informed of the content of the lead standard, and a training program must be initiated. Training is required each year, and the employer must make available to all employees a copy of the OSHA lead standard and its appendixes (29 CFR 1910.1025(l)).

National Institute for Occupational Safety and Health Criteria

NIOSH was created in 1970 by the OSHAct and established in the Department of Health Education and Welfare, which became the Department of Health and Human Services, to carry out the duties of the OSHAct assigned to the secretary of health and human services. Those duties include research, experiments, and demonstrations related to occupational safety and health (Public Law 91-596). NIOSH first published its *Criteria for a Recommended Standard: Occupational Exposure to Inorganic Lead* in 1973. After an OSHA proposal to revise the occupational health standard for inorganic lead in 1976, NIOSH revised its criteria document in 1978 and lowered its recommended 10-hour TWA for airborne lead from 150 to 100 µg/m^3 and its recommended maximum BLL from 80 to 60 µg/dL (NIOSH 1978).

NIOSH noted that testimony at OSHA hearings indicated that "based on about 10 studies . . . to keep blood lead levels in male workers below 40

[µg/dL], air lead exposures have to be kept under 50 µg/m^3" (NIOSH 1978, p. XII-14). In addition, data from the General Motors plant in Muncie, Indiana, indicate that "if yearly average personal sampler air lead exposure . . . is kept below 100 µg/m^3, yearly average blood leads in over 90% of workers will be under [60 µg/dL]. Similarly, if yearly average personal sampler air leads . . . are kept under 50 µg/m^3, yearly average blood leads will be 40 [µg/dL] or lower for over half of the workers. One of the greatest impacts of reducing lead exposure in air from 200 to 100 µg/m^3 is a great increase in the number of workers with blood lead levels 40 [µg/dL] or lower" (NIOSH 1978, p. XII-15).

NIOSH also notes that the relationship between air lead and BLL may not be linear over the whole range of exposures: "Incremental changes in air lead exposure in the range up to 100 µg/m^3 produce greater increases in blood lead than do similar increases in the range from 100-200 µg/m^3" (NIOSH 1978, p. XII-115).

At the time, the OSHA proposal was for an action level of 50 µg/m^3, which NIOSH endorsed in its criteria document "as a future goal to provide greater assurances of safety" (NIOSH 1978, p. XII-19). That air level would keep BLLs at about 40 µg/dL or lower in virtually all workers, protecting against "subclinical" effects of lead. NIOSH also endorsed a "vigorous medical surveillance program" for workers exposed above the action level but below the proposed maximum air lead concentration of 100 µg/m^3. NIOSH estimated that "even at the proposed air standard of 100 µg/m^3, less than half of the workers will have blood lead levels above 40 [µg/dL]" (NIOSH 1978, p. XII-19).

In 1997, NIOSH published a *Federal Register* notice (62 Fed. Reg. 55407 [1997]) requesting comments and information relevant to the potential health risks associated with occupational exposure to inorganic lead at or below the OSHA PEL of 50 µg/m^3. To date, however, no additional recommendations have been proposed by NIOSH.

American Conference of Governmental Industrial Hygienists Guidelines

ACGIH is a not-for-profit organization with a mission for advancing occupational and environmental health and safety through the development and publication of scientific guidelines and research. The organization manages several scientific committees that consist of volunteers in government agencies, academic institutions, labor unions, and industrial companies. The committees are the Threshold Limit Values for Chemical Substances Committee, which develops TLVs for airborne chemical substances and materials; the Biological Exposure Indices (BEIs®) Committee for biologic indicators of exposure to chemical substances and materials; and the Threshold Limit Values for Physical Agents Committee, which recommends guidelines for physical hazards, such as noise, temperature, and pressure. Each committee recommends exposure guidelines to the ACGIH Board of Directors, which ensures that all organizational procedures and policies have been followed before ratification. The recommen-

dations of those three committees are published annually in a guide, and written documentation for each TLV and BEI is also prepared.

The lead BEI was first proposed by ACGIH in 1985 and adopted in 1987. Levels were set for lead concentrations in blood (50 µg/dL), urinary creatinine (150 µg/g), and ZPP in blood (250 µg/dL for erythrocytes or 100 µg/dL for blood after 1 month of exposure). In 1995, a new BEI BLL was adopted for lead (30 µg/dL); other indicators in urine and blood were dropped. A notation B (background) was included, indicating that "the determinant may be present in biological specimens collected from subjects who have not been occupationally exposed, at a concentration which could affect interpretation of the result. Such background concentrations are incorporated into the BEI value" (ACGIH 2012). In 1998, the B notation was removed "because the U.S. population average blood lead concentration . . . is now less than 3 [µg/dL]" (ACGIH 2001a, p. 8).

The goal of the current BEI for lead in blood is to lower the likelihood of several adverse health outcomes, including

- Psychologic and psychomotor effects that appear to occur at BLLs over 30 µg/dL.
- Changes in nerve conduction and latency intervals that appear to occur at BLLs over 30 µg/dL.
- Decrements in hematologic reserve capacity (one study) at BLLs over 40 µg/dL.
- Increased blood pressure and incidence of hypertension; effects at BLLs under 30 µg/dL expected to be very small.
- Renal impairment with minor effects reported at BLLs under 30 µg/dL and increased proteinuria at BLLs of 40 µg/dL.
- Spontaneous abortions and effects on male fertility that appear to occur at BLLs over 30 µg/dL.
- Decreased length of gestation and decreased birth weight; expert reviews indicate that effects appear to be associated with BLLs over 30 µg/dL.

ACGIH (2001a) notes that some studies have found effects at levels below the BEI, but these were short-lived, did not affect functional capacity, or were contradicted by other studies. The documentation also notes that women and men of childbearing potential who have BLLs over 10 µg/dL may be at risk for having a child who has levels greater than the current guideline from the Centers for Disease Control and Prevention, 10 µg/dL.

A TLV 8-hour TWA of 150 $\mu g/m^3$ for lead and inorganic compounds in air was first adopted in 1946 and has undergone several revisions. The most recent revision in 1995 recommended a TLV-TWA of 50 $\mu g/m^3$. ACGIH classifies lead as a confirmed animal carcinogen with unknown relevance to humans. The TLV-TWA was based on the ACGIH BEI for lead and "intended to minimize the potential for adverse health effects that may include blood dyscrasias, reduced nerve conduction velocities, peripheral neuropathies, a possible kidney

dysfunction, spermatogenesis, impaired intellectual development in children exposed to lead during gestation, and carcinogenicity" (ACGIH 2001b, p. 1). ACGIH notes that "blood values, rather than work environment air lead concentrations, are most strongly related to health effects. . . . The TLV-TWA is intended to maintain worker blood lead levels below the BEI of 30 µg/dL. Maintaining blood levels at or below this level must also focus on control of exposure to non-airborne sources of lead, such as by meticulous plant environment housekeeping, strict personal cleanliness, and prohibition of eating, drinking, and smoking in lead-contaminated areas" (ACGIH 2001b, p. 1).

Derivation of the appropriate air lead concentration used the steepest slope (0.19 µg/dL of blood per µg/m^3 of air) found in the literature (slopes ranged from 0.03 to 0.19 µg/dL of blood per µg/m^3 of air). A TLV-TWA of 50 µg/m^3 would be expected to result in a BLL of about 9.5 µg/dL. ACGIH proposes that this air concentration will be sufficient to prevent a BLL of 30 µg/dL (the BEI) if other sources (community or noninhalation workplace exposures) are adequately controlled.

GUIDELINES OF OTHER COUNTRIES

European Council Directive 98/24

The European Council Directive 98/24/EC of 1998 on the protection of the health and safety of workers from risks related to chemicals has "binding occupational exposure limit values" (a maximum allowable TWA of lead in air) and "binding biological limit values and health surveillance measures" (BLLs that should not be exceeded) for lead (Council 1998). The binding occupational exposure limit is 150 µg/m^3 (8-hour TWA), and the biologic limit is 70 µg/dL. Medical surveillance is indicated if a worker is exposed to lead at 75 µg/m^3 (TWA over a 40-hour week) or if a worker's BLL is over 40 µg/dL. Taylor et al. (2007) conducted a survey of how the directive has been implemented in 14 EU countries and found disparities in its implementation. Most of the countries have implemented the binding occupational exposure limit for lead, but five countries (Denmark, Finland, France, Germany, and Poland) have set lower limits. Most countries have established binding biologic limits lower than the one specified in the directive, with a range of 20-60 µg/dL. Two countries (Belgium and the Netherlands) allow BLLs as high as 80 µg/dL provided that other measures of biologic effects are below certain limits. Most of the 14 EU countries have adopted the directive's biologic triggers for medical surveillance.

European Union Scientific Committee on Occupational Exposure Limits

The European Union Scientific Committee on Occupational Exposure Limits (SCOEL) recommends a lower biologic limit for lead than European

Council Directive 98/24/EC of 1998. The SCOEL recommends a BLL of 30 µg/dL to prevent adverse neurobehavioral effects and signs of male reproductive toxicity that occur at BLLs of 40 µg/dL and higher. The SCOEL could not identify a threshold for impairment of cognitive development in newborns and infants and indicated that "exposure of fertile women to lead should . . . be minimised" (SCOEL 2002, p. 13).

The European Union also has an 8-hour TWA of 100 µg/m^3 for inorganic lead, including lead fumes and dusts with particle sizes below 10 µm. The SCOEL documentation conclusion that the carcinogenicity of lead most likely depends on "indirect, rather than on direct genotoxic mechanisms" implies a "practical threshold for the carcinogenic effects, and would argue in favour of the possibility of setting a health-based OEL [occupational exposure limit] for lead" (SCOEL 2002, pp. 8-9). The air lead concentration is considered consistent with the biologic limit and was derived from field studies of lead-battery workers by Lai et al. (1997) and others (e.g., Kentner and Fischer 1994).

German Commission for the Investigation of Heath Hazards of Chemical Compounds in the Work Area

The Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) is in the Deutsche Forschungsgemeinschaft (German Research Foundation), a private organization for science and research. The commission is responsible for determining the current state of research regarding workplace hazardous-chemical health risks and for advising public authorities about these risks. The MAK Commission proposes MAK values (maximum concentrations at the workplace) and BAT values (biologic tolerance values) for volatile chemicals and dusts and proposes procedures for analyzing these substances. Each year, the MAK and BAT proposals are presented to the German federal minister of labor and social affairs; these are reviewed by the ministry's Committee on Hazardous Substances, which determines whether they should be included in the Hazardous Substances Ordinance. The MAK Commission also develops and publishes detailed scientific documentation for each of its MAK and BAT values.

From 1977 to 2006, the German MAK for lead and inorganic compounds was 100 µg/m^3 (inhalable). The cancer classification was 3B (evidence of carcinogenicity in animal or in vitro studies without sufficient evidence for classification in other categories). The BAT, adopted in 2000, was 40 µg/dL in blood, with a pregnancy-risk group B notation (probable risk of damage to embryo or fetus even when the BAT or biologic guideline value [BLW] is observed). Those levels were expected to protect men and women from central nervous system effects, which are first seen at average BLLs of 40 µg/dL, and to prevent cognitive deficits in offspring of exposed women. There was no clear threshold for the latter; effects were expected to be minimal if maternal BLLs were under 30 µg/dL (DFG 2009).

After a 2006 reclassification of inorganic lead compounds as category 2A carcinogens (probably carcinogenic in humans) by the International Agency for Research on Cancer, a German category 2 cancer notation was assigned to these compounds, and the MAK and BAT were withdrawn. German policy states that "substances carcinogenic in man or experimental animals are classified in categories 1 or 2 and are not assigned MAK or BAT values." Thus, there is no longer a German MAK for lead, because "it is not possible to derive a no observed adverse effect level for the clastogenic effect of lead and its inorganic compounds. . . . Therefore, no threshold value can be established" (DFG 2009, p. 188).

A BLW is used when a BAT value cannot be established, as for carcinogenic or suspected carcinogenic substances. The BLW for lead is 40 µg/dL for all men and women older than 45 years old and 10 µg/dL for women younger than 45 years old. The bases for those values are the prevention of neurotoxic effects and minimization of reproductive toxic effects (DFG 2005). Lead and its inorganic compounds are considered to be in pregnancy-risk group B, which indicates probable risk of damage to an embryo or fetus even when the BLW is observed.

United Kingdom Health and Safety Executive

The Health and Safety Executive (HSE) enforces the Health and Safety at Work Act of 1974, the primary legislation governing occupational health and safety in the UK. The HSE is a nondepartmental public body with Crown status and is accountable to the ministers of the Department for Work and Pensions. The HSE regulates work-related health and safety in the UK in partnership with local authorities; its mission is the prevention of workplace death, injury, and ill health. Within the HSE, the Health and Safety Laboratory is responsible for research, scientific, and forensic services, including technical support of investigations.

In 2002, the UK HSE issued updated guidance regarding the Control of Lead at Work Regulations (HSE 2002). Workplace exposure to lead is considered significant if levels exceed half the occupational exposure limit of 150 $\mu g/m^3$ for lead other than lead alkyls, there is substantial risk of ingestion of lead, or there is risk of skin exposure to forms of lead that are readily absorbed through the skin. Significant exposures require protective clothing for employees, air monitoring, and employee medical surveillance. Where engineering controls are not feasible or effective, respiratory protection is required. High standards of personal hygiene—including washing facilities and policies that forbid eating, drinking, or smoking in lead-contaminated areas—are required for all employees.

The HSE guidance notes that "there is not necessarily a strong relationship between the amount of lead the body absorbs and the concentration of lead-in-air" (p. 8). Medical surveillance is required for those who have significant air lead exposures. If an employee's BLL exceeds the action level (see below), the

employer must immediately determine the cause, review controls, and take steps to reduce it. If the BLL exceeds the suspension level, the employee should be removed from work.

The action levels are

a. BLL of 25 µg/dL in women of reproductive capacity.
b. BLL of 40 µg/dL in people 16 or 17 years old.
c. BLL of 50 µg/dL in any other employee.

The suspension levels are

a. BLL of 30 µg/dL or urinary lead adjusted for creatinine of 25 µg/g in women of reproductive capacity.
b. BLL of 50 µg/dL in young people not of reproductive capacity.
c. BLL of 60 µg/dL or urinary lead adjusted for creatinine of 110 µg/g in any other employee.

The guidance states that "some employees, excluding women of reproductive capacity, who have worked for many years in the lead industry, may have built up a high body burden of lead which could take a long time to fall below the suspension level of 60 µg/dL" (p. 70). They include employees who "a) have been employed on work which exposed the employee to lead for at least 20 years or b) are aged 40 years or more and may have been employed on work involving exposure to lead for at least 10 years" (p. 70). In those cases, "the employer may take some additional factors into account in deciding whether they should be taken off work involving exposure to lead" (p. 71), including the following:

1. Employees who meet either of the above conditions before 2002 may continue to work if BLLs are maintained under 80 µg/dL and ZPP levels are under 20 µg/g of hemoglobin, or ALAD levels are above 6 European units or aminolevulinic acid levels in urine (ALAU) are under 20 mg/g of creatinine.
2. Employees who meet either of the above conditions after 2002 may continue to work if BLLs remain under 70 µg/dL and ZPP levels are under 20 µg/g of hemoglobin, or ALAD levels are above 6 European units or ALAU levels are under 20 mg/g of creatinine.

It is important to note that the regulation prohibits employment of young persons and women in some tasks in lead smelting and refining and in lead-acid battery manufacturing.

EXPOSURE-ASSESSMENT METHODS

The committee evaluated the exposure assessment methods used by the Department of Defense (DOD) for air sampling. This section describes the re-

quirements of the OSHA lead standard and contrasts them with the methods used by DOD.

Occupational Safety and Health Administration Requirements

The OSHA lead standard (29 CFR 1910.1025) includes requirements for performing monitoring to measure employee exposures and to determine the sources of lead emissions. The standard requires that the monitoring be performed without regard to respirators, that is, the protective factor of any worn respirator cannot be used in the determination of the exposure of an employee (43 Fed. Reg. 52925 [1978]).

The lead standard requires an initial assessment of lead exposures and requires that air sampling be performed or that air sampling performed in the previous 12 months be used to make the initial determination of employee exposure. The standard indicates that the air monitoring can be conducted on a sample of the exposed workers who are believed to have the highest exposures. Any additional monitoring is contingent on the findings of the initial assessment.

If the results of the initial assessment are negative (airborne concentrations were all below the action level of 30 $\mu g/m^3$), no further monitoring is required. The results of the initial assessment need to be documented in writing. Further monitoring needs to be conducted only if a change in the process, controls, or personnel could result in an increased exposure to lead.

When the initial assessment indicates that personal exposures exceed the action level, additional monitoring is required. If measured exposures are between the action level and the PEL, monitoring must be performed every 6 months. If measured exposures are above the PEL, monitoring must be performed quarterly. Quarterly monitoring must continue until at least two sets of consecutive monitoring results are below the PEL.

Department of Defense Methods

DOD goes beyond the OSHA requirements of assessing the exposures of a sample of the exposed workers who have the highest lead exposures. It has incorporated the American Industrial Hygiene Association (AIHA®) Exposure Assessment Strategy. The strategy was first published in 1991 in *Strategy for Occupational Exposure Assessment*. The strategy was updated, and a second edition was published in 1998. The current third edition, *A Strategy for Assessing and Managing Occupational Exposures*, was published in 2006 (Bullock and Ignacio 2006).

The purpose of AIHA's Exposure Assessment Strategy is to protect the health of workers by managing current and future risks with a program that is efficient and effective. The strategy uses a small number of samples (generally six to 10) to determine that worker exposures are acceptable or unacceptable or that more information is needed. The strategy involves placing workers into

similar exposure groups that perform the tasks or jobs in the same manner and therefore are expected to have similar exposures. Monitoring can be performed on the different similar-exposure groups so that acceptability can be judged. The AIHA Exposure Assessment Strategy requires personal exposures to generally be less than 10% of the PEL (or other standard being used) for a judgment of acceptability. The strategy potentially results in lower estimated exposures of workers (Bullock and Ignacio 2006).

ADDITIONAL CONSIDERATIONS

Creation of the OSHA lead standard for general industry in the late 1970s was an important advance over occupational exposure limits that already existed. The OSHA standard is complex and includes more than the setting of a PEL or an action level. For example, air monitoring will not adequately capture lead exposures that occur via noninhalation routes, which can be important in firing ranges. In particular, ingestion of lead is of concern because of deposition of lead aerosols on hands during shooting or secondary hand contamination after contact with surfaces on which lead aerosols have collected or settled.

There are no data that directly link hand or surface contamination levels with specific BLLs, but studies have demonstrated that improved hygiene practices for both employees and the environment can lead to decreasing BLLs. Scott et al. (2012) found that although ventilation is an important method for controlling lead exposures, housekeeping can also have a substantial effect on lead contamination on surfaces in and around a shooting range. Even in ranges that have good ventilation and that use ammunition with lead-free primers, poor housekeeping or failing to decontaminate the range thoroughly before switching primers may adversely affect lead exposures. The Navy Environmental Health Center notes in its *Indoor Firing Ranges Industrial Hygiene Technical Guide* (NEHC 2002) that although there are no established limits for surface contamination in workplaces, OSHA (1993) has indicated in a compliance instruction for the construction industry (CPL 2-2.58) that an acceptable lead loading for nonlead work areas should be 200 $\mu g/ft^2$. Appendix D of the Navy technical guide suggests clearance standards of 200 $\mu g/ft^2$ for interior floors and horizontal surfaces and 800 $\mu g/ft^2$ for exterior concrete (the latter is derived from an interim recommendation from the US Department of Housing and Urban Development).

It has been shown that high BLLs can result from lead ingestion during smoking and eating with lead-contaminated hands. Sato and Yano (2006) found that BLLs were substantially higher in battery-recycling employees whose hands showed lead contamination. In a longitudinal study of lead-battery employees in Taiwan, Chuang et al. (1999) found that smoking at work more than 3 days per week increased BLLs by 3.08 μg/dL compared with BLLs in those who had never smoked at work ($p < 0.05$). Although this is not statistically significant, mean BLLs were 1.32 μg/dL higher in employees who ate at work compared

with those who did not ($p = 0.082$). Employees who both smoked more than 3 days per week and ate at work were almost 3 times as likely to have high BLLs than employees who did not.

Recent investigations have demonstrated that washing with soap and water is not an effective method for removing lead from skin. Sato and Yano (2006) demonstrated, using sodium sulfide to detect contamination by a change in skin color, that skin-color changes were more likely in lead-battery recycling employees who did not wash their hands or bathe beforehand or who had higher BLLs. Esswein et al. (2011) also developed a colorimetric method capable of detecting lead on skin and workplace surfaces. They demonstrated that hand decontamination, rather than washing, is required to ensure complete removal of lead. They found that a mixture of isostearoamidopropyl morpholine lactate and citric acid applied with a textured absorbent material was almost 100% effective in removing lead from skin. They suggest that the best method for preventing hand-to-mouth exposure may be skin decontamination and a colorimetric method to detect remaining contamination.

If DOD's occupational exposure limit for lead is lowered, surface and skin decontamination are likely to play an even more important role in effective control of employee exposures than in the past. It will be important for an updated guideline to address the importance of decontamination in more detail and with greater precision. Where possible, quantitative levels of contamination should be included in guidelines rather than qualitative statements regarding the importance of housekeeping.

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3

Toxicokinetics of Lead

This chapter presents an overview of the exposure considerations for lead that are relevant to firing ranges, including an overview of the routes of exposure, factors that affect internal doses of lead, and exposure factors that influence health outcomes.

Several terms are used differently by toxicologists and epidemiologists, so definitions are provided for terms as they are used here. *Dose* is the amount of a substance to which a person is exposed over some period. An *exposure dose* is how much of a substance is encountered in the environment. An *absorbed dose* or *internal dose* is the amount of a substance that gets into the body through the eyes, skin, stomach, intestines, or lungs. One needs to differentiate exposure (lead outside the body) from the internal dose.

HOW EXPOSURE BECOMES DOSE

On a firing range, exposure to lead arises through two primary media: air and surfaces. Absorption in general can occur through four primary routes: inhalation, ingestion, transdermal, and percutaneous. The latter two routes are not relevant to firing ranges, because inorganic lead is not normally absorbed through the skin, nor is lead injected percutaneously in this setting. Concerning the inhalation route, particle size is an important determinant of internal dose. Smaller particles, like those associated with fumes (under 0.1 μm in aerodynamic diameter), have large relative surface areas and are generally better absorbed than larger particles by both the inhalation and ingestion routes. Fume and particles under 5 μm are also inhaled more deeply into the lungs and are better absorbed than larger particles at the alveolar-capillary interface. However, smaller fume particles may agglomerate into larger particles before inhalation or ingestion. About 50% of the lead deposited in the respiratory tract is absorbed and reaches the systemic circulation whereas net absorption of ingested lead from the adult digestive tract is appreciably lower (less than 8% to 10%) (O'Flaherty 1993).

Juhasz (1977) qualitatively demonstrated that lead-based ammunition was associated with the generation of particles ranging from under 0.3 to 100 μm; most of the particles were smaller than 1 μm. That observation is similar to results regarding the particle size of copper associated with the use of lead-based or lead-free frangible ammunition. For example, the Air Force Institute for Occupational Health (AFIOH 2008) reported that most airborne copper particles associated with an M4 rifle muzzle blast have an aerodynamic diameter under 5 μm. The committee was unable to obtain similar quantitative data on particle size distributions associated with lead-based ammunition used in different small-arms weapons.

The basis of the general industry lead standard of the Occupational Safety and Health Administration (OSHA) and a large scientific literature (IARC 2006; ATSDR 2007; EPA 2012; NTP 2012) document that several personal behaviors can increase lead dose, including tobacco-smoking, eating, and drinking in the workplace and inadequate personal hygiene before leaving the workplace. The OSHA standard therefore mandates no eating, drinking, or smoking in areas that have potential lead exposure and separate facilities for changing clothes and washing before returning home.

TOXICOKINETIC CONSIDERATIONS

The toxicokinetics of lead—that is, its absorption, distribution, metabolism, and excretion—and its relevance to common biomarkers of exposure are schematically represented in Figure 3-1.

Understanding lead's partitioning in the body provides a useful background for understanding the available biomarkers of lead. After gastrointestinal or pulmonary absorption, lead enters the bloodstream, in which the vast majority of circulating lead (over 95%) is bound to erythrocyte proteins and the remainder is associated with the plasma (Barltrop and Smith 1972; Cake et al. 1996; Bergdahl et al. 1997), before reaching target organs. Lead is distributed widely in the body and can gain access to sites in the central and peripheral nervous, cardiovascular, renal, reproductive, musculoskeletal, hematopoietic, and other organ systems (see reviews by Hu et al. 2007; EPA 2012; NTP 2012). Lead binds to sulfhydryl and carboxyl groups on a wide variety of structural and functional proteins (Rabinowitz et al. 1973), thereby altering their structure or function. Lead can also agonize or antagonize calcium and thereby alter its normal metabolic functions (Rabinowitz 1991). The ability to mimic calcium contributes to lead storage in the bone; at equilibrium, lead-exposed persons have a substantial body burden of lead: over 90% in the bone pool, 2-8% in various soft tissues, and 2-5% in blood (Rabinowitz et al. 1976). In addition, lead's nonspecific binding to a variety of proteins and its involvement in calcium pathways explain in large part its myriad health effects. Lead is excreted primarily in urine; this pathway can be enhanced by intravenous chelating agents, such as calcium disodium ethylene diamine tetraacetic acid (commonly referred to as

$CaNa_2EDTA$), and oral chelating agents, such as 2,3-dimercaptosuccinic acid (commonly referred to as DMSA) (Graziano et al. 1985). A much smaller proportion of absorbed lead is excreted in feces, sweat, breast milk, seminal fluid, and hair.

A number of factors can influence the toxicokinetics of lead. Several aspects of nutrition—including iron, zinc, and calcium status and supplementation—can influence the gastrointestinal absorption and distribution of lead. Diets low in calcium or high in lactose or fat have been reported to enhance lead accumulation (Goyer 1995). Studies have shown that iron-deficient children have higher gastrointestinal absorption of lead (Barton et al. 1978). Sex differences in lead toxicokinetics have also been reported. Some studies have shown that blood lead levels (BLLs) varied by geographic areas, were higher in men than in women, and were higher in smokers than in nonsmokers (Friberg and Vahter 1983). Analysis of BLLs in monozygotic and dizygotic twins provided evidence of a genetic factor's regulating BLLs in females but not in males (Bjorkman et al. 2000). Yang et al. (2007) reported a small but statistically significant increase in BLLs of about 7.6% from a baseline of 2.64 µg/dL in teenage girls during menstruation, but the underlying factors related to this observation remain unknown. Lactating and postmenopausal women can mobilize lead stores from bone (Hernandez-Avila et al. 2000; Ettinger et al. 2004).

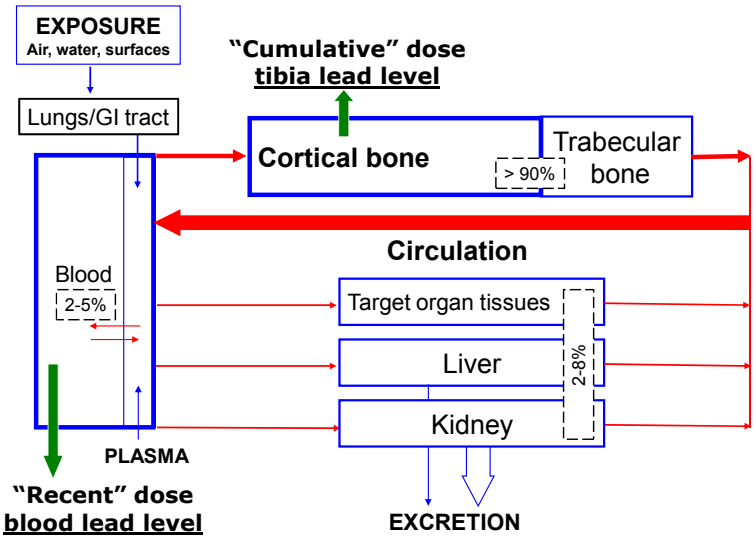

FIGURE 3-1 Compartmental model for lead (modified from O'Flaherty 1993). The percentages shown represent the fractions of lead found in different tissue compartments. Used with permission of Brian Schwartz, Johns Hopkins Bloomberg School of Public Health.

A number of genetic polymorphisms can influence the toxicokinetics of lead (Wetmur et al. 1991; Wetmur 1994; Lee et al. 2001a; Hu et al. 2007). A large number of genetic polymorphisms have been studied in relation to lead, including polymorphisms of the delta-aminolevulinic acid dehydratase (*ALAD*), the vitamin D receptor (*VDR*), apolipoprotein E (*APOE*), Na^+,K^+-ATPase, endothelial nitric oxide synthase (*eNOS*), and human hemochromatosis protein (*HFE*) genes. The two best-studied polymorphisms are those of the *ALAD* and *VDR* genes, which are relatively common; the less common allele is present in 5-25% of people, depending on race and ethnicity (Lee et al. 2001b). In a number of study populations and designs, the $ALAD^2$ allele has been associated with higher BLLs (although recent studies with lower average BLLs are inconsistent on this point [Krieg et al. 2009]), lower DMSA-chelatable lead levels, lower zinc protoporphyrin levels for a given BLL, lower plasma aminolevulinic acid levels (Sithisarankul et al. 1997), and a variety of renal effects (Smith et al. 1995). In addition, there is evidence that the $ALAD^2$ allele may contribute to selection factors: it has been associated with longer work duration in the lead industry and is more prevalent in factories that have higher exposure to lead (Schwartz et al. 1995). In studies of lead workers, the *VDR B* allele has been associated with higher blood pressure (Lee et al. 2001b), tibia lead, DMSA-chelatable lead, and BLL (Schwartz et al. 2000a), and there are different associations of age and work duration with tibia lead levels (Schwartz et al. 2000b). Thus, there is compelling evidence that genetic polymorphisms modify the toxicokinetics of lead. However, the committee agreed with a prior review that concluded that "although recent studies suggest that polymorphisms in specific genes may modify the toxicokinetics [of lead] . . . research findings at present are insufficient to conclusively identify genotypes that confer increased [health] risk" (Kosnett et al. 2007, p. 464).

The committee believed it important to note that the studies of gene-lead interaction, although providing interesting and compelling mechanistic information, must be considered in relation to prevailing ethical and policy contexts. It is standard practice in the United States and around the world to develop occupational exposure and dose standards that protect all workers, including the most susceptible, rather than to perform genetic screening and exclude higher-risk people from work settings.

MEASURING INTERNAL LEAD DOSE

Because of its wide distribution in the body, biologic measures of lead dose in a number of tissues—including blood, plasma, umbilical cord blood, hair, fingernails and toenails, breast milk, urine, semen, soft tissue, and bone—are available (see review by Hu et al. 2007). The excretion of lead in urine can be enhanced by $CaNa_2EDTA$ or DMSA, and chelatable lead has been used to estimate lead dose (Schütz et al. 1987; Tell et al. 1992; Lee et al. 1995, 2000; Schwartz et al. 2001). Because $CaNa_2EDTA$ can partially chelate bone lead

stores, EDTA-chelatable lead has been used as a surrogate for cumulative dose in some studies, but this is probably inadequate. DMSA chelates lead primarily from soft tissues, so DMSA-chelatable lead has been offered as an estimate of soft-tissue lead stores (Lee et al. 1995, 2000; Schwartz et al. 2001).

Lead in whole blood is typically measured with atomic absorption spectrophotometry or other analytic techniques (Hu et al. 2007). In a one-compartment pharmacokinetic model, blood lead has an average elimination half-life of 30 days (Rabinowitz 1991) and is therefore thought to represent primarily variation in recent exposure but in equilibrium with bone lead stores (Hu et al. 2007). Lead can be measured in trabecular bone (such as patella, calcaneus, or finger phalanx) or cortical bone (such as tibia) with several techniques. In general, measurement of bone lead (in micrograms of lead per gram of bone mineral) with ^{109}Cd K-shell x-ray fluorescence (XRF) has the greatest antemortem utility (Todd et al. 1992; Landrigan and Todd 1994; Todd and Chettle 1994), although XRF is a research tool and is not generally available for clinical or medical surveillance. Lead in patella has complex elimination kinetics with three phases of elimination; the longest clearance half-time is about 5-7 years (Kim et al. 1997). In contrast, lead in tibia has a clearance half-time of 25-30 years (Chettle et al. 1991; Todd and Chettle 1994), although recent longitudinal studies suggest that it may be considerably longer (Wilker et al. 2011). Thus, it is not surprising that patella lead and tibia lead have shown different associations with health outcomes in some studies—evidence that the former's generally shorter elimination kinetics may make it inadequate for estimating lifetime dose (Hu et al. 2007).

DOSE-RESPONSE CONSIDERATIONS

In 1978, when the OSHA lead standard was first promulgated, the average American had a BLL of about 15 µg/dL (CDC 1982; Annest et al. 1983). OSHA consequently set an occupational provision that a single BLL over 60 µg/dL or three BLLs averaging over 50 µg/dL would result in the medical removal of a worker until the BLL was under 40 µg/dL on two occasions. BLL is the preferred dose metric for studying health outcomes that are thought to be *short-latency, acute health effects due to recent exposure*. However, in persons who had high past exposures, BLL can also be moderately increased because of its equilibrium with bone lead stores. BLL may thus also reflect, to some degree, longer-term doses. In contrast, associations of health outcomes with cumulative blood lead index (CBLI, the area under the curve of blood lead vs time, Figure 3-2) or tibia lead concentrations are the preferred dose metrics for studying *longer-latency, chronic health effects of cumulative dose*. OSHA, however, did not consider lead bioaccumulation (in bone) and did not distinguish between short-latency, acute health effects and longer-latency, chronic health effects when setting the 1978 lead standard.

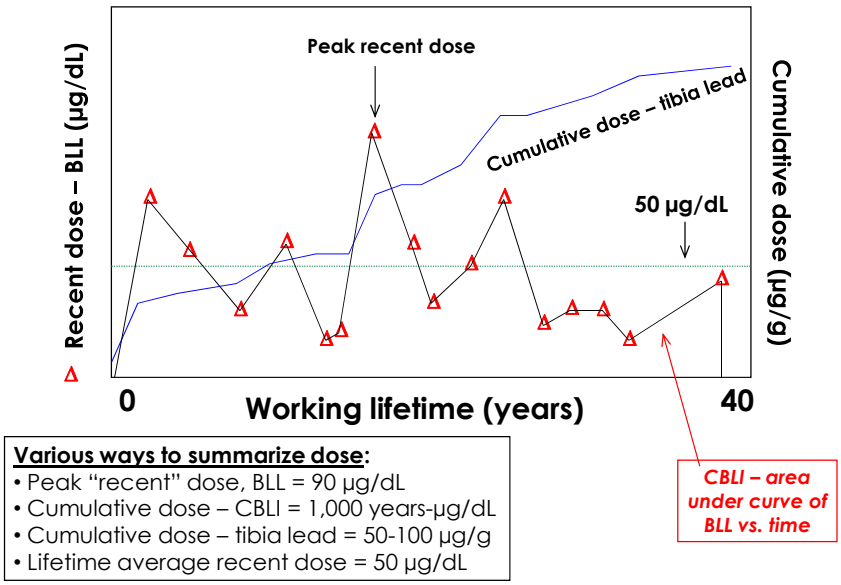

FIGURE 3-2 Schematic of a hypothetical worker's dose over time. Used with permission of Brian Schwartz, Johns Hopkins Bloomberg School of Public Health.

Figure 3-2 illustrates additional complexities in relating lead dose to health outcomes. BLLs are highly variable throughout the work span, reflecting variation in exposure, the shorter elimination time from the blood compartment, and changes in work practices, hygiene, and related issues. Such data can be summarized in a variety of ways, but many health studies have relied on a single BLL in relation to health effects. Peak levels, average levels, and current levels could be expected to have different associations with health outcomes, depending on mechanism of action, latency, and other considerations. For some health outcomes, such as pregnancy, there are critical exposure periods during which a given lead dose could have a much greater deleterious effect than if it occurred at other stages of life. As the working lifetime increases and cumulative dose steadily rises, bone lead stores contribute more to current BLLs, so a single BLL later in the working career can reflect exposure earlier in employment, when BLLs may have been much higher. Thus, a single BLL measurement late in employment or at higher ages may reflect both recent external exposure and cumulative exposure. Finally, the CBLI can be estimated when rich longitudinal BLL data are available. Studies have validated the CBLI as an estimate of lifetime dose because it correlates strongly with tibia lead levels and its associations with health outcomes are more similar than BLL to the associations observed with tibia lead (Roels et al. 1995; Somervaille et al. 1988; Landrigan and Todd 1994).

Given the importance of cumulative lead dose to health (discussed in Chapters 4 and 5) and the lack of wide availability of XRF systems for measuring bone lead, this argues that more frequent longitudinal monitoring of BLLs, with attention to the CBLI over time, would have much greater utility than heretofore required under the OSHA lead standard.

PHARMACOKINETIC MODELS FOR LEAD

The relationship between air lead concentration and BLL is complex. Exposure to lead can occur through multiple pathways. BLL is the exposure metric most commonly described in association with health effects in humans, and lead exposure is typically assessed by using a pharmacokinetic model to relate air (or dietary) exposure concentrations to BLLs. The committee's goal was not to review in depth the various dosimetry models available for lead but to explore how dosimetry models were used in the development of the OSHA general industry lead standard and to evaluate the models and their assumptions (see Table 3-1).

In the late 1970s, OSHA sought the development of a dosimetry model that could predict the distribution of BLLs in a given worker population in response to changing air lead concentrations. To that end, OSHA commissioned the development of a model by the Massachusetts Institute of Technology Center for Policy Alternatives (CPA) (Ashford et al. 1977; 43 Fed. Reg. 52962 [1978]). CPA used a physiologic model (developed by S. R. Bernard) to describe the response of BLLs to air lead exposure. Bernard constructed a kinetic model that included blood, bone, liver, kidney, and soft tissue compartments. Each compartment contained a variable-size "pool" of lead that was determined by metal transfer across compartment boundaries. Lead exchange across each compartment was represented as a first-order rate constant (in a transport-limited or diffusion-limited model). Transfer rate constants in the CPA model were obtained from experimental measurements of retention and excretion of lead in dogs, rats, baboons, and humans. A series of exponential equations were then generated to predict the time-dependent accumulation of lead in a compartment given a presumed air concentration. The relationship between BLL and air lead concentration (Figure 3-3) was given by the following equation (43 Fed. Reg. 52962 [1978]):

$$\text{BLL} = a(\text{air lead concentration}) + b,$$

where a is the BLL-air lead slope coefficient and b is the BLL at zero air lead. The coefficients a and b varied with job tenure.

TABLE 3-1 Assumptions Used by Occupational Safety and Health Administration for Center for Policy Alternatives Model and Committee's Evaluation

Parameter	Assumptions	Committee Evaluation
Particle size	First 12.5 μg/m^3 of airborne lead consisted of lead particles with an aerodynamic diameter of ≤1 μm; remainder consisted of larger particles (≥1 μm) that would be deposited in upper respiratory tract.	Size of lead aerosol can influence deposition and absorption of lead from respiratory tract and delivery to systemic bloodstream (Froines et al. 1986; Park and Paik 2002). For example, lead fumes are more easily absorbed from lungs and result in higher BLLs than inhalation of larger lead particles. Smaller lead particles also appear to be more soluble regardless of chemical form of dust (Spear et al. 1998).
Deposition efficiency	37% of all lead particles ≤1 μm are deposited in alveolar region. CPA model assumes that alveolar deposition of particles ≥1 μm does not occur.	It is now generally accepted that some alveolar deposition occurs with particles of 1-10 μm (Froines et al. 1986; ACGIH 2012).
Lung and gastrointestinal absorption	Complete (100%) absorption occurs in alveolar region. In contrast, larger particles (>1 μm) would be removed by mucociliary clearance and swallowed, and about 8% of lead would be absorbed in gastrointestinal tract.	Bioavailability of lead is influenced by chemical speciation, age of exposed person, level of lead exposure, matrix, and nutritional status of person.
Model linearity	Nonlinearity captured by using time-dependent mathematical terms.	Some models assume linearity in relationship between intake parameters and BLL. Available data suggest that relationship between BLL and lead intake is nonlinear (Leggett 1993). At low lead concentrations, kinetics are linear; nonlinear kinetics start when lead concentration in erythrocytes reaches 60 μg/dL, which corresponds to BLL of about 25 μg/dL (Leggett 1993).
Contributions from other routes of exposure	Inhalation exposure considered	It is critical to consider oral exposure to lead-based dusts during training and weapon cleaning.

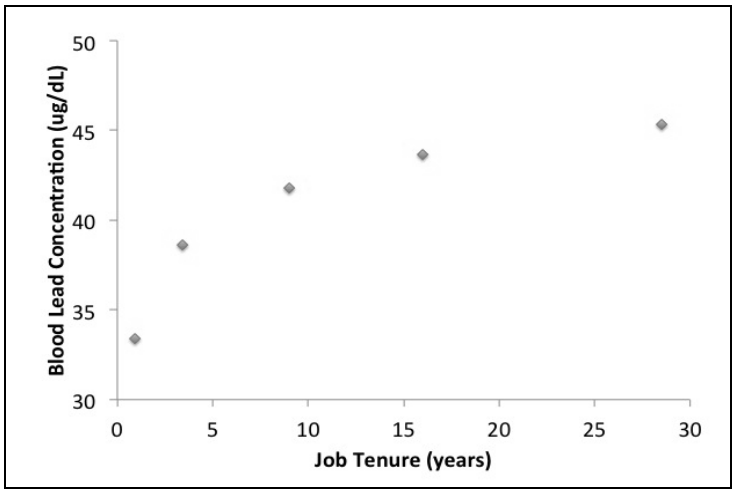

FIGURE 3-3 Time-dependent relationship between BLL and air lead concentration as estimated with the CPA model used by OSHA to develop the permissible exposure level. Estimated BLLs for lead workers exposed to airborne lead at 50 μg/m^3.

The CPA model had several key assumptions (referred to as assumption C in Table 1 of the OSHA documentation). On the basis of those and other assumptions, the model predicts that 70% of lead-exposed workers would have a BLL under 40 μg/dL and 6% would have a BLL over 50 μg/dL (Snee 1982).

Several additional models have been developed to describe the relationship between air and BLLs. Their general form accounts for multiple sources of lead exposure and follows this relationship:

$$\text{BLL} = A[(\text{air lead concentration}) + (B_1\{\text{food lead concentration}\}) + (B_2\{\text{water lead concentration}\})]^K,$$

where terms A, B_n, and K are derived from the data.

"Validation" of those models uses a variety of databases, two of which were from exposure studies by Azar et al. (1975) and Williams et al. (1969). In both studies, exposure durations were assumed to be sufficient to result in pseudo-steady-state BLLs. The Williams et al. study surveyed lead-acid battery factory workers and included the use of personal samplers. Personal samplers were worn for 2 weeks, and daily BLLs were determined for each worker during the second week. Personal lead exposures varied between job categories and ranged from 9 to 218 μg/m^3. Mean BLLs varied between job categories and ranged from 27.2 to 74.2 μg/dL.

Snee (1982) provides equations based on the best fit to the Williams dataset. When it is applied to an air lead concentration of 50 μg/m^3, the resulting

BLL is estimated to be 35 μg/dL, which shows good concordance with the CPA model used by OSHA. Fleming et al. (1999) reported the following relationship between BLL and air lead concentration for a population of Brunswick smelter workers:

$$BLL = 16.1[(0.24\{\text{Air Lead Concentration}\} + (\{0.76\}\{0.5\}) + 1.65]^{0.379},$$

where the background air lead concentration is assumed to be 0.5 $\mu g/m^3$. Application of that model to an air lead concentration of 50 $\mu g/m^3$ predicted a BLL of about 44 μg/dL. This result is also in good agreement with the model used by OSHA.

The committee recognizes that dosimetry models may need to be developed for firing-range personnel. Multiple models, including physiologically based pharmacokinetic (PBPK) models for lead, could be used for this purpose (O'Flaherty 1991a,b,c; 1993; 1995; Beck et al 2001). PBPK models allow experimental or environmental levels of exposure (or "applied dose") to be re-expressed more usefully as corresponding levels of biologically effective concentrations in target tissuess that would potentially be affected by toxicity. PBPK models can be used to estimate corresponding levels of exposure associated with different BLLs of concern. Statistical and Monte-Carlo methods can also be used to estimate values of PBPK model parameters and to characterize uncertainty in PBPK model predictions.

LEAD DOSE AND HEALTH

For its evaluation of health effects associated with lead exposure in Chapters 4 and 5, the committee sought to find evidence that health effects could occur at exposures and doses lower than those specified in the OSHA lead standard. OSHA relied most heavily on BLLs, so the committee evaluated studies first for their associations of health effects with BLLs. Because the evidence base on health effects related to cumulative dose was insufficient in the 1970s, OSHA's consideration of exposure duration and cumulative dose was inadequate. The committee therefore had to distinguish between BLL associations that were probably acute effects of recent dose from those in which BLLs were acting as surrogates for longer dose periods because of long exposure durations or higher exposure intensities in the past. The committee's primary focus was on health effects that occur at BLLs under 40 μg/dL for short-duration exposures and on acute health effects. For longer-duration exposures and chronic health effects, BLLs had to be extrapolated in the context of what is known about tibia lead, CBLIs, and exposure duration. In evaluating relationships of the dose measures with health outcomes, dose-response relationships were evaluated, when available, for important characteristics, such as thresholds, U-shaped relations, log-linear relations, and linearity, especially in the dose range of interest.

The presence of log-linear relationships was deemed particularly important; they were emphasized in this report because they imply much greater incremental health risks with increasing lead dose at low levels than at higher levels.

An important assumption of the OSHA lead standard was that a population of workers exposed at OSHA's permissible exposure limit (PEL) would have an average BLL of 40 µg/dL; that is, the PEL was selected to keep BLLs around 40 µg/dL on the average. Thus, if the committee found evidence to suggest that health effects occur below that BLL (or below the CBLIs or tibia lead levels that would result over time from long-duration BLLs at lower levels), it would have to conclude that the OSHA exposure standard is inadequate. Although OSHA did not explicitly address the issue of cumulative dose, another important implication of the OSHA standard, in allowing a BLL of 40 µg/dL for a working lifetime of 40 years, is that OSHA believed that this was an acceptable cumulative dose. As previously discussed, cumulative lead dose has most commonly been measured with the CBLI (in micrograms per deciliter times years of exposure [µg-years/dL]) or tibia lead. Although it was not explicitly stated, the OSHA lead standard presumes that a CBLI of 1,600 µg-years/dL (average BLL of 40 µg/dL × 40 years) provides adequate protection for lead workers. Although there is some uncertainty on this point, even if the most conservative estimates are used (Healey et al. 2008), that CBLI is roughly equivalent to tibia lead of 40-80 µg/g (on the basis that tibia lead can be estimated as 2.5-5% of the CBLI) (Hu et al. 2007; Healey et al. 2008). Thus, an important question is whether there is evidence that a CBLI under 1,600 µg-years/dL or a tibia lead concentration of 40-80 µg/g may be associated with adverse effects in lead workers.

A large and growing scientific literature documents a number of factors that modify the health effects of lead and make some people more susceptible to the effects of lead than others. For example, the decrement in cognitive function with higher tibia lead concentration is more severe in those who have the *APOE* ε-4 allele (Stewart et al. 2002). Other such factors include a number of genetic polymorphisms, coexposures (including noise for hearing loss), and comorbidities (Hu et al. 2007). Of those, only coexposure to noise was explicitly considered by the committee. Noise is an important coexposure on firing ranges and was identified by the Department of Defense as an appropriate factor to consider in addressing the committee's charge. The other factors were not considered relevant, because the military population is typically healthy, having undergone medical screening that would minimize the likelihood that firing-range workers would have medical conditions that would make them more susceptible to lead (such as high blood pressure and diabetes mellitus).

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4

Noncancer Health Effects

The adverse effects of lead on human health are well documented. Effects seen after lead exposure depend on the exposure dose and the absorbed dose, the duration of exposure, the timing of exposure during critical life stages, and host factors. The committee used the recent compilations of the toxicologic and epidemiologic studies of lead performed by the National Toxicology Program (NTP) and the US Environmental Protection Agency (EPA). Those reviews were used as a basis for identifying the primary noncancer health end points that would be of concern for firing-range personnel, including adverse effects on the adult nervous, hematopoietic, renal, reproductive, immune, and cardiovascular systems. Adverse effects in the developing fetus were also of concern. This chapter is organized along those lines.

As noted in Chapters 1 and 2, the committee specifically sought health-effects data on blood lead levels (BLLs) under 40 μg/dL because the current standard of the Occupational Safety and Health Administration (OSHA) aims to maintain BLLs below that concentration. Evidence on health effects at a corresponding estimated cumulative blood lead index (CBLI) of 1,600 μg-years/dL (that is, 40 years at 40 μg/dL) and tibia lead levels of 40-80 μg/g were also specifically sought.

ENVIRONMENTAL PROTECTION AGENCY AND NATIONAL TOXICOLOGY PROGRAM ASSESSMENTS

Three previous assessments were used by the committee for identifying key literature: the 2012 *NTP Monograph on Health Effects of Low-Level Lead*, the 2006 EPA *Air Quality Criteria Document [AQCD] for Lead*, and the 2012 EPA *Integrated Science Assessment for Lead (Second External Review Draft)*. Each of the assessments provides background on lead exposure and lead toxicokinetics and includes a review of the primary epidemiologic or experimental literature for evidence that lead exposure is associated with adverse health effects. NTP's assessment focuses on epidemiologic evidence at BLLs of under 5 or under 10 μg/dL and presents specific conclusions regarding each category of

health effect. EPA's *AQCD* (2006) also identified health effects associated with BLLs under 10 μg/dL. EPA's *Integrated Science Assessment for Lead* (2012) affirmed many of the conclusions reached in the *AQCD* (2006). The reader is referred to specific conclusions reached by those organizations and the committee's conclusions with respect to their relevance to Department of Defense personnel who work on firing ranges. The committee also performed its own search for recent relevant literature on the health effects of lead to supplement those evaluations.

NEUROLOGIC EFFECTS

The adult nervous system is a critical target for the toxic effects of lead. Effects on the central nervous system of lead workers include dose-related changes in cognitive and psychomotor performance and mood, neurodegenerative diseases, and neurophysiologic changes in the auditory, visual, and balance systems. Effects of occupational lead exposure on the peripheral nervous system at BLLs of 60-70 μg/dL are manifested as motor weakness with abnormalities in motor and sensory nerve conduction. No peripheral motor or sensory symptoms are known to occur at BLLs under 40 μg/dL, but sensory nerve function is associated with lead dose.

Potential modes of action for lead neurotoxicity include oxidative stress, inhibition of enzymes needed for energy production, decreased levels of neurotransmitters and altered neurotransmitter release, and increased permeability of the blood-brain barrier (EPA 2012). Ultimately, lead-induced neurotoxicity in adults consists of changes in brain structure and neurochemistry, including white-matter changes, reduction in gray matter, and alterations in brain metabolites.

Conclusions from the Environmental Protection Agency 2006 and 2012 and National Toxicology Program 2012 Lead Documents

Environmental Protection Agency 2006 *Air Quality Criteria Document*

EPA's 2012 *Integrated Science Assessment for Lead (Second External Review Draft)* focused on updating the 2006 *Air Quality Criteria Document for Lead* (EPA 2006), so a summary of the key neurotoxic effects of lead in adults from the earlier document will be presented first.

Studies of the effects of aging and their relationship with environmental lead exposure included the Veterans' Administration Normative Aging Study established in 1961 in Boston and consisting of 2,280 healthy men 21-80 years old who are examined every 3 years (Payton et al. 1998; Rhodes et al. 2003; Wright et al. 2003; Weisskopf et al. 2004), the Kungsholmen Project on aging and dementia in Sweden (Nordberg et al. 2000), and the third National Health and Nutrition Examination Survey (NHANES III) (Krieg et al. 2005). There was

mixed evidence of a relationship between environmental lead exposure, as judged by current BLL, and impaired cognitive performance in adults. However, when bone lead was used as the measure of lead dose, the Normative Aging Study found significant associations with impaired neurocognitive performance. Bone lead measurements capture both long-term cumulative exposure and past high lead exposure, which may be more important than current BLL.

In contrast, EPA noted that occupational lead exposure measured by BLL, CBLI, and bone lead was associated with decreased cognitive and psychomotor performance, diminished peripheral sensory nerve function, slowing in visual evoked potentials and brainstem auditory evoked potentials, and abnormalities in postural sway. Evidence in support of EPA's conclusion included onset of diminished cognitive function and diminished psychomotor speed at a BLL of 18 μg/dL (Schwarz et al. 2001). However, in some studies, it was not the current BLL (under 30 μg/dL) but the measures of CBLI or bone lead concentration that were associated with poorer neurobehavioral performance (Lindgren et al. 1996; Bleecker et al. 1997; Hänninen et al. 1998; Bleecker et al. 2005a). The same relationship was found for peripheral sensory nerve studies most commonly associated with CBLI (Chia et 1996a,b; Kovala et al. 1997; Yokoyama et al. 1998). Changes in sensory nerve function occurred at BLLs of 28-30 μg/dL (Chuang et al. 2000; Bleecker et al. 2005b). Visual evoked potentials, measuring speed of conduction in the optic nerves, were prolonged beginning at BLLs of 17-20 μg/dL (Abbate et al. 1995). Slowed brainstem auditory evoked potentials were found to be associated with CBLI or weighted average BLL (Discalzi et al. 1992, 1993, Bleecker et al. 2003). A calculated benchmark dose for postural sway (measure of balance) was a current BLL of 14 μg/dL (Iwata et al. 2005).

EPA identified a few publications that reported an increased risk of amyotrophic lateral sclerosis (ALS) and motor neuron disease associated with past occupational lead exposure (Roelofs-Iverson et al. 1984; Armon et al. 1991; Gunnarsson et al. 1992; Chancellor et al. 1993; Kamel et al. 2002). The presence of the delta-aminolevulinic acid dehydratase (ALAD) 2 allele ($ALAD^2$) increased that risk (odds ratio [OR] = 1.9; 95% confidence interval [CI]: 0.60, 6.3) (Kamel et al. 2003). Essential tremor, another neurodegenerative disorder, was associated with low concurrent BLL (3 μg/dL) caused by exposure to environmental lead (Louis et al. 2003), but there was no information about past exposures, which might have been higher. The presence of the $ALAD^2$ allele increased the odds of essential tremor by a factor of 30 compared with subjects that had only the $ALAD^1$ allele (Louis et al. 2005).

Environmental Protection Agency 2012 *Integrated Science Assessment for Lead (Second External Review Draft)*

Neurobehavioral and Mood Effects

EPA (2012) reviewed epidemiologic evidence of associations between environmental lead exposure and neurobehavioral outcomes primarily from two

studies—the Baltimore Memory Study and the Normative Aging Study. Results of those studies strengthened the association between cognitive performance and bone lead and probably reflect the effect of cumulative lead exposure on the brain (Shih et al. 2006; Weuve et al. 2006; Wang et al. 2007; Weisskopf et al. 2007; Rajan et al. 2008; Bandeen-Roche et al. 2009; Glass et al. 2009). Analysis of data from NHANES III revealed an association between concurrent BLL and lower neurobehavioral performance in particular age and genetic-variant subgroups (Krieg and Butler 2009; Krieg et al. 2009, 2010). Mood disorders in young adults in the survey increased with a BLL of 2.11 μg/dL or above (Bouchard et al. 2009). However another publication that used data from NHANES III but was not included in the EPA 2012 document examined all adults (20 years old or older) and found no consistent relationship between environmental lead exposure and depression (Golub and Winters 2010).

In adults who had past occupational lead exposure, BLL and bone lead were associated with decrements in cognitive performance years after the cessation of occupational exposure. The relationship between bone lead and cognitive performance was significant in workers older than 55 years old (Khalil et al. 2009a).

Neurodegenerative Disease

Two case-control studies published after 2006 found that BLL was associated with ALS, but EPA had concerns about the contribution of "reverse causality". ALS decreases the ability to move the limbs, and this leads to increased demineralization of bone and release of lead from bone, which in turn increase BLLs. Thus, the disease could cause the increased BLL. In addition, there was bias in the study in that survival time increased with higher BLLs (Kamel et al. 2008; Fang et al. 2010). Parkinson disease was also reported to be associated with bone lead and whole-body lifetime exposure (Coon et al. 2006; Weisskopf et al. 2010), but EPA commented on the need to establish temporality between exposure and the onset of the disease and on the potential contribution of past exposure to manganese, a metal known to be associated with parkinsonism. Two additional studies reported the association of BLL and essential tremor, but the temporality between exposure and development of tremor was not established (Dogu et al. 2007; Louis et al. 2011)

Sensory Organ Function

New analyses have found an increase in hearing thresholds associated with bone lead in subjects in the Normative Aging Study (Park et al. 2010). In the occupational setting, people who had higher BLLs had significantly greater hearing loss (Chuang et al. 2007; Hwang et al. 2009).

National Toxicology Program 2012 *Monograph on Effects of Low-Level Lead*

A recent NTP report examined the literature of neurotoxic outcomes associated with a BLL under 10 µg/dL. NTP concluded that the evidence that BLLs under 10 µg/dL were associated with the diagnosis of essential tremor was sufficient but that the evidence that BLLs under 5 µg/dL were associated was limited. NTP also found limited evidence of an association between BLLs under 10 µg/dL and impaired cognitive function in older adults, psychologic effects, ALS, and reduced sensory function and auditory function. There were no studies of an association between BLLs of 10 µg/dL or lower and Alzheimer disease, Parkinson disease, or sensory function or visual function.

Neurobehavioral and Mood Effects

NTP noted that studies of BLL and cognitive performance in older adults who had environmental lead exposure had mixed results (Payton et al. 1998; Nordberg et al. 2000; Wright et al. 2003; Gao et al. 2008). According to data from NHANES III, neurobehavioral test performance in younger adults had no significant relationship with BLL (Krieg et al. 2005, 2009). However, studies that reported no association between neurologic outcome and BLL often found decreased neurobehavioral performance significantly associated with BLL (Weisskopf et al. 2004; Shih et al. 2006; Weuve et al. 2009). BLLs were associated with psychiatric symptoms and mood disorders in young and older adults (Rhodes et al. 2003; Rajan et al. 2007; Bouchard et al. 2009). NTP concluded that the evidence was limited because of the small number of studies and because there were multiple studies of a given cohort. However, as with all outcomes in adults, NTP noted that there were no data on whether BLLs were always under 10 µg/dL from birth until the time of study.

Neurodegenerative Effects

NTP had the same concern as EPA (2012) that the association of BLL with ALS was influenced by reverse causality and by bias due to the increase in survival time with higher BLL (Kamel et al. 2008; Fang et al. 2010). NTP's conclusion that there was sufficient evidence of an association between essential tremor and BLLs under 10 µg/dL was based on case-control studies conducted in two countries (Louis et al. 2003, 2005, 2011; Dogu et al. 2007). The evidence that essential tremor is associated with a BLL of 3 µg/dL is based on a small sample (300 essential tremor patients) in the two studies. Thus, NTP concluded that evidence of an association with a concurrent BLL under 5 µg/dL was limited.

Sensory Organ (Auditory) Effects

In occupational studies, diminished hearing occurred primarily at frequencies over 3,000 Hz and began at a BLL of 7 µg/dL (Chuang et al. 2007; Hwang et al. 2009). The pattern of hearing loss was not the typical pattern seen in noise-induced hearing loss. The authors concluded that BLLs under 10 µg/dL might enhance noise-induced hearing loss. In people who had environmental lead exposure, hearing loss was associated with bone lead (Park et al. 2010).

Other Studies Considered

Mood and Occupational Lead Exposure

Mood is evaluated with a neurologic-symptom questionnaire and a mood checklist or mood scale, such as the Center for Epidemiological Studies Depression Scale (CES-D) and the Profile of Mood States (POMS), which screen on moods such as anger, confusion, depression, fatigue, anxiety and tension, and vigor. Those mood-rating scales differ slightly in content depending on the country in which they were developed. Mood change might be a primary outcome associated with exposure, but its evaluation is also necessary in administering neuropsychologic testing, inasmuch as mood may influence performance. In some occupational studies, mean BLLs of 29-43 µg/dL were associated with POMS subscales or items on a mood checklist (Maizlish et al. 1995; Hänninen et al. 1998; Niu et al. 2000), whereas other studies found no relationship between BLLs of 27-38 µg/dL and measures of mood (Stollery et al. 1989; Chia et al. 1997; Osterberg et al. 1997; Lucchini et al. 2000). Results of administration of the CES-D screen for depression to 803 lead-exposed Korean workers were significantly associated with tibia lead (mean 37 µg/g) but not with BLL (mean 32 µg/dL) after adjustment for covariates (Schwartz et al. 2001).

In some studies, difficulty in concentrating, irritability, fatigue, and muscle and joint pain were reported in workers who had a mean BLL of 43 µg/dL (Maizlish et al. 1995) or 27 µg/dL (Lucchini et al. 2000), whereas other studies with mean BLLs in the high 30s found no association with symptoms (Chia et al. 1997; Osterberg et al. 1997). Lucchini et al. (2000) estimated a BLL threshold of 12 µg/dL for a statistically significant increase in neurologic symptoms.

Neurobehavioral Effects

Tests are often used in neurobehavioral batteries to measure effects of lead exposure in different domains, such as attention and concentration (Digit Span), conceptual and executive functioning (Stroop and Trails B), visuoperceptive and visuoconstructive (Block Design), visuomotor (Reaction Time, Pegboard Test, Digit Symbol Substitution, and Trails A), verbal memory (Rey Auditory Verbal

Learning Test, Logical Memory, and Paired Associated Learning), and nonverbal memory (Rey-Osterreith Complex Figure and Benton Visual Retention). In analyzing the association between lead exposure and test performance, adjustment for confounders is critical. Confounders include age, education (preferably a measure of verbal intelligence), depressive symptoms, alcohol use, and smoking.

A study by Lindgren et al. (1996) of 467 Canadian lead-smelter workers was one of the first to evaluate the effects of cumulative lead exposure on the nervous system. The mean number of years of employment was 18, the mean BLL was 28 μg/dL, the time-weighted average BLL over a working lifetime was 40 μg/dL, and the mean CBLI was 765 μg-years/dL. CBLI exposure groups differed significantly in digit symbol, logical memory, Purdue dominant hand, and Trails A and B. No dose-effect relationship between BLL and neuropsychologic performance was found. In the smelter population, 256 currently employed workers had a median score of 29 (range 19-30) in the screening test called the Mini-mental State Examination (MMSE). A dose-effect relationship between CBLI and MMSE was found only in the 78 workers who had a reading grade level less than 6 in the Wide Range Achievement Test (Revised). The absence of a dose-effect relationship in workers who had higher reading grade levels and the same CBLI was attributed to increased cognitive reserve (Bleecker et al. 2002). An in-depth examination of verbal learning and memory in the same population found no association with BLL, but with increasing CBLI or time-weighted average BLL over a working lifetime there was poorer storage and retrieval of previously learned verbal material. Alterations in the ability to organize materials in long-term memory interfered with retrieval efficiency. Those changes occurred in the group that had a mean time-weighted-average BLL of 41.2 ± 11.09 μg/dL and a CBLI of 813.1 ± 409.68 μg/g (Bleecker et al. 2005a). The one test sensitive to BLL in the population was Simple Reaction Time (SRT), which had a curvilinear relationship with increasing reaction time beginning at a BLL of about 30 μg/dL (Bleecker et al. 1997).

Hänninen et al. (1998) studied neuropsychologic effects in lead-battery workers who had current BLLs under 50 μg/dL compared with those who had BLLs over 50 μg/dL in the past. They found that overall high, past exposure had the greatest effect on tests that required the encoding of complex visually presented stimuli. The authors concluded that the effect of lead on brain function is better reflected by the history of the BLL, such as the CBLI, than by bone lead content.

Some studies, particularly cross-sectional ones, that included measures of cumulative lead and current lead exposures found the strongest association between BLL and neurobehavioral performance when the concurrent BLLs were high. Schwartz et al. (2001) reported that bone lead concentration was not associated with neurobehavioral performance in 803 Korean lead-exposed workers. In contrast, lead-exposed workers performed significantly worse than controls on SRT, Digit Span, Benton Visual Retention, Colored Progressive Matrices,

Digit Symbol, and Purdue Pegboard after controlling for age, sex, and education. BLL was the best predictor of significant decrements in neurobehavioral performance on Trails B, Purdue Pegboard (four measures), and Pursuit Aiming (two measures). For those effects, an increase in BLL of 5 μg/dL was equivalent in its effects to an increase of 1.05 years in age. Use of Lowess lines for Purdue Pegboard (assembly) and Trails B suggested a threshold BLL of 18 μg/dL.

Hwang et al. (2002) evaluated 212 consecutively enrolled workers from the above cohort of 803 Korean workers for protein kinase C (PKC) activity and the relationship between BLL and neurobehavioral performance. BLLs of 5-69 μg/dL were significantly associated with decrements in Trails B, SRT, and Purdue Pegboard (three measures). PKC activity was measured by back-phosphorylation of erythrocyte membrane proteins and found not to be associated with neurobehavioral test scores. However, dichotomization at the median revealed significant effect modification; the association of higher BLLs with poorer neurobehavioral performance occurred only in workers who had lower back-phosphorylation levels (which correspond to higher in vivo PKC activity). The authors suggested that PKC activity may identify a subpopulation at increased risk for neurobehavioral effects of lead.

The cohort of Korean lead workers was studied longitudinally. The relationship between occupational lead exposure and longitudinal decline in neurobehavioral performance was assessed in 576 current and former Korean lead workers who completed testing at three visits at about yearly intervals (Schwartz et al. 2005). Cross-sectional associations of BLL and short-term change occurred with Trails A and B, Digit Symbol, Purdue Pegboard (four measures), and Pursuit Aiming after adjustment for covariates. However, longitudinal BLL was associated only with poorer performance on Purdue Pegboard (four measures). Tibial bone lead was associated with Digit Symbol and Purdue Pegboard (dominant hand). For those effects, the effect of an increase in lead concentration from the 25th to the 75th percentile was equivalent to an increase of 3.8 years of age for cross-sectional BLL, 0.9 year of age for historical tibia lead, and 4.8 years for longitudinal BLL.

Long-term effects of occupational lead exposure have been evaluated in other studies. Khalil et al. (2009a) evaluated 83 lead-exposed workers and 51 controls 22 years after their initial neuropsychologic evaluation when the mean BLL was 40 μg/dL in workers and 7.2 μg/dL in controls. Twenty-two years later, their mean BLLs were 12 and 3 μg/dL, respectively. Mean bone lead obtained only at followup was 57 μg/g in workers and 12 μg/g in controls. BLL was not associated with any of the scores in five cognitive domains. Peak tibia lead was calculated to reflect bone lead level at the time that lead exposure ended. Peak bone lead predicted lower cognitive performance and cognitive decline over 22 years. A statistically significant association of peak bone lead with performance on spatial ability, learning and memory, and total cognitive score was found only in workers who were over 55 years old. The results support a decline in cognitive performance with aging in lead-exposed workers.

Brain Anatomic and Biochemical Effects

Eighty workers at the primary lead smelter previously described by Lindgren et al. (1996) underwent magnetic resonance imaging (MRI) of the brain. MRIs were graded by a neuroradiologist for white matter change (WMC) on a scale of none to lesions larger than 10 mm. Only the 61 workers under 50 years old were used in the analysis because of the large effect of age on WMC. Mean BLL in the group was 29 µg/dL, CBLI was 826 µg-years/dL, and bone lead was 39 µg/g. Logistic regression of WMC on lead exposure after controlling for age, hypertension, triglycerides, C-reactive protein, smoking, and drinking found CBLI and bone lead significantly associated with WMC. A measure of psychomotor speed and dexterity, grooved pegboard, was significantly related to WMC and measures of lead exposure. Path analysis supported that the effect of CBLI and bone lead on psychomotor speed and dexterity was mediated by WMC (Bleecker et. al. 2007).

Magnetic resonance spectroscopy (MRS) of the brain was used to examine the biochemical changes caused by lead (Hsieh et. al. 2009). Twenty-two lead workers (mean BLL 16.99 µg/dL, tibia lead 61.55 µg/g, and patella lead 66.29 µg/g) in a paint factory were compared with 18 healthy volunteers (mean BLL 3.4 µg/dL, tibia lead 18.51 µg/g, and patella lead 7.14 µg/g). Measures that reflected neuronal loss and myelin alterations were lower in the lead-exposed workers primarily in the frontal and occipital lobes. Multiple linear regression for each MRS measure and lead after adjustment for sex, age, and smoking found significant associations of increasing BLL and bone lead levels with decreases in gray and white matter in the occipital lobe. The strongest of the associations was of neuronal loss in the frontal lobe with BLL and patella lead level. It was suggested that those changes may contribute to poorer outcome in tests of memory and visual performance.

Peripheral Nerve Function

A meta-analysis of 32 publications of nerve-conduction studies and occupational lead exposure found BLL to be a weak predictor of peripheral nerve impairment (Davis and Svendsgaard 1990). Nerve-conduction testing includes analysis of latent period (time it takes for stimulatory impulse to initiate an evoked potential), conduction velocity, and amplitude. Reduced nerve-conduction velocities in lead-exposed subjects revealed that the median motor nerve was most sensitive.

Nerve-conduction studies of workers in a lead-battery factory (Kovala et al. 1997) found that sensory amplitudes of the median and sural nerves correlated negatively with long-term exposure (CBLI and duration of exposure). Chia et al. (1996b) also found the strongest dose-effect relationship between median sensory conduction velocity and CBLI, whereas He et al. (1988) found sensory-

conduction abnormalities related to BLL. Yokoyama et al. (1998) measured the distribution of conduction velocities in large myelinated fibers of the sensory median nerve twice (at a 1-year interval) in 17 gun-metal workers. They reported that measurements of chelatable lead (readily mobilized lead from soft tissue) were more strongly predictive of peripheral nerve impairment than BLL.

Other studies examined peripheral sensory nerve function in the extremities with a quantitative sensory test, vibration threshold, that measures the integrity of large myelinated nerve fibers. Kovala et al. (1997) found vibration threshold at the ankle to be related to CBLI and duration of exposure, whereas finger vibration threshold was associated with BLL (mean BLL 26 μg/dL and average BLL over the preceding 3 years 29 μg/dL). Overall, historical BLLs were more closely associated with peripheral nerve function than was bone lead in this population. In contrast, Schwartz et al. (2001) examined vibration thresholds and bone lead in 803 Korean workers and 135 controls and found that after adjustment for covariates tibia lead concentration (mean 37 μg/g) but not BLL (mean 32 μg/dL) was significantly associated with poorer vibration threshold in the dominant great toe but not the finger. In a followup study of 576 lead workers who completed three visits at yearly intervals, vibration threshold in the toe was associated with current BLL (mean 31 μg/dL), longitudinal BLL, and tibia lead (38 μg/g) after adjustment for covariates (Schwartz et al. 2005). Chuang et al. (2000) reported on vibration perception in the foot in 206 lead-battery workers. There was a significant association of BLL in the past 5 years (mean 32 μg/dL) and time-weighted average BLL over a working lifetime (mean 32 μg/dL) with vibration perception in the foot after adjustment for covariates, including the use of vibrating hand tools. Data analyses used a hockey-stick regression that uses two different curves to fit two regions of a dataset (Hudson 1966). The curve of foot vibration threshold vs mean BLL for the preceding 5 years showed an inflection point around 30 μg/dL; a positive linear relation above this point suggested a potential threshold.

Bleecker et al. (2005b) examined peripheral nerve function in 80 smelter workers with Current Perception Threshold (CPT), a neuroselective test that measures integrity of the large and small myelinated nerve fibers and unmyelinated nerve fibers. CPT was not associated with BLL (mean 26 μg/dL) or bone lead (mean 40 μg/g). CPT for large myelinated nerve fibers had a curvilinear relationship with time-weighted average BLL over a working lifetime (mean 42 μg/dL), with an apparent threshold at 28 μg/dL. In regression analyses, CBLI and its associated exposure variables explained the increasing variance in CPT of large myelinated fibers and suggested that cumulative lead exposure intensity is more important than duration of exposure with regard to the peripheral nervous system. At the highest BLL criterion, both large and small myelinated nerve fibers were impaired. Ergonomic stressors (used as a surrogate for active motor units) enhanced the effect of lead on the peripheral nervous system.

Evoked Potentials

Visual evoked potentials (VEPs) and brainstem auditory evoked potentials (BAEPs) measure speed of conduction in the nerves that run from the eyes and ears, respectively, to the relevant locations in the brain. On stimulation, nerves send signals in the form of "waves" that can be detected, and the time it takes for an impulse to initiate an evoked potential is latency. The VEP is the first positive wave and usually occurs at 100 ms (P100 latency) after the visual stimulus. That measure is very sensitive to demyelination of the optic nerve. BAEPs also have discrete waveforms. Wave I arises from the auditory nerve, and its latency reflects peripheral transmission time; wave III is generated predominantly from the auditory pathway in the lower brainstem; and wave V is generated from the upper brainstem. The use of interpeak latencies helps distinguish changes in peripheral auditory nerve latency from changes in brainstem transmission in the auditory pathway.

Abbate et al. (1995) studied VEPs in 300 lead-exposed men (30-40 years old) in good health who had no other neurotoxic exposure. Their BLLs ranged from 17 to 60 μg/dL and were stratified into four groups for data analyses. P100 latency of VEPs was significantly prolonged in all the BLL groups. Prolonged VEP began at BLLs of 17-20 μg/dL. The contribution of age was not a concern, and careful screening ruled out other medical and eye conditions and other potential exposures.

BAEPs in 49 lead-exposed workers (mean BLL 55 μg/dL; time-weighted average BLL over a working lifetime 54 μg/dL) and in age- and sex-matched controls were recorded (Discalzi et al. 1992). In workers who had a time-weighted average BLL over 50 μg/dL, conduction in the entire brainstem was slower. In a later publication, Discalzi et al. (1993) reported identical results in 22 battery storage workers who had a mean BLL of 47 μg/dL and a time-weighted average BLL of 48 μg/dL.

BAEPs were measured in 359 currently employed smelter workers who had mean indexes of exposure of 17 years, BLL of 28 μg/dL, and CBLI of 719 μg-years/dL (Bleecker et al. 2003). Linear regression, adjusted for age, found that BLL was significantly associated with peripheral auditory nerve conduction speed and CBLI was significantly associated with lower brainstem conduction speed. Groups were created on the basis of BAEP scores greater than clinical cut-off scores for peripheral auditory nerve conduction speed and brainstem conduction speed. For groups that had abnormal clinical BAEP values, the mean range of BLLs was 28.3 (± 7.8) to 34.8 (± 6.44) μg/dL and of CBLI was 723.0 (± 438.47) to 934.0 (± 352.80) μg-years/dL. Those results were all significantly higher than the ones in the group that had normal BAEPs.

A case-control study in Taiwan (Chuang et al. 2007) in which workers received periodic health examinations found 121 people who had hearing thresholds above 25 dB and 173 controls who had normal hearing. Geometric mean

BLL was 10.7 µg/dL for cases and 3.9 µg/dL for controls. In the final regression model with all-six-frequency thresholds for both ears, significant predictors of hearing loss were age and lead concentration (logarithmically transformed). Years of noise exposure at work had a nonsignificant, weak effect. The net effect of lead is 7.11 dB above the pooled all-six-frequency thresholds for both ears when logarithmically transformed lead level is increased by 0.1 µg/dL. Exposure to manganese or arsenic did not contribute to the model, but selenium was found to be protective against lead ototoxicity.

Another Taiwanese study (Hwang et al. 2009) examined 259 workers in a steel plant with audiograms and blood studies of lead, manganese, copper, zinc, arsenic, and cadmium. Noise levels were established in all work areas. Mean BLL was 5.43 µg/dL. Logistic regression adjusting for age and noise exposure found that BLLs of 7 µg/dL or higher were associated with hearing loss at sound frequencies of 3,000-8,000 Hz ($p < 0.005$ to $p < 0.05$). The OR was largest for 4,000 Hz (6.26) and 8,000 Hz (6.16). The pattern of hearing loss beginning with the greatest loss was 6,000 Hz, 4,000 Hz, 8,000 Hz, and 3,000 Hz—not the typical pattern for noise-induced hearing loss with a "notching" of the audiogram at 4,000 Hz. The authors conclude that BLL under 10 µg/dL may enhance noise-induced hearing loss.

Postural Stability

Postural sway measures balance or steadiness on a force platform that requires integration of visual, vestibular, and peripheral sensory inputs and motor output. No standard protocol is used among studies.

One approach to determining the critical dose of lead that affects postural balance in the occupational setting is the benchmark-dose method in which a concentration of lead results in an increased probability of an abnormal end point—a benchmark response—and thereby places exposed people at increased risk (Iwata et al. 2005). Iwata et al. (2005) defined their benchmark dose level as the 95% lower confidence limit of the benchmark dose. In 121 lead-exposed workers who had a mean BLL of 40 µg/dL, almost all sway measures were significantly larger than those in controls. The mean benchmark dose level of the current BLL for postural sway was 14.3 µg/dL.

Postural sway evaluated in 49 chemical workers exposed to lead stearate (mean BLL 18 µg/dL, average working lifetime BLL 24 µg/dL, and mean CBLI 391 µg-years/dL) and 23 controls found significant increases in the exposed group in sway in all directions at high and low frequencies with eyes open and closed (Yokoyama et al. 1997). After adjustment for covariates, dose-dependent associations were observed between BLL and sway in the anterior-posterior direction and between time-weighted average BLL and right to left sway. The authors concluded that changes in the vestibulocerebellar pathways are affected by BLL whereas the anterior cerebellar lobe pathways are affected by time-weighted average BLL.

Postural sway characteristics were measured in 60 lead storage battery workers (mean BLL 36 µg/dL) and 60 controls (mean BLL 6 µg/dL). Computerized postural sway measurements showed that lead workers had poorer postural stability and that it decreased when their eyes were closed, but this deterioration in performance was not associated with BLL (Chia et al. 1994). A second publication examined cumulative BLL over 10 years and found that CBLI for the 2 years before testing was associated with all postural sway measures with eyes closed (Chia et al. 1996b).

When postural control was measured in 63 lead battery workers (mean past BLL 38 µg/dL), there were statistically significant increases in mean body oscillations with eyes closed and head tilted forward (Ratzon et al. 2000). Partial correlation after adjustment for education, coffee consumption, hours of sleep, and estimate of health was significant only for total lead exposure and increased body oscillations with head tilted forward. To maintain balance, lead-exposed workers required increased oscillations when visual and vestibular inputs were altered.

Autonomic Function and Electroencephalography

Effects on cardiac parasympathetic functioning were found in autonomic nervous system testing of 172 lead-exposed workers who had a mean BLL of 36 µg/dL (Teruya et al. 1991). A significant dose-related decrease in R-R interval (interval between the peak of one heart beat to the next) during deep breathing was reported in 132 workers who had a stable BLL over the preceding year. The decrease was most notable at BLLs of 30 µg/dL or higher, with a possible mild decrease first occurring at BLLs of 20 µg/dL or higher. Niu et al. (2000) reported similar findings in 44 lead-exposed workers who had a mean BLL of 29 µg/dL.

Sympathetic nerve function as seen in variations in R-R interval on electrocardiography and changes in finger blood flow with postural changes according to Doppler flowmetry were measured in 128 workers in the ceramic painting industry (mean BLL 13 µg/dL). The 46 workers in the lowest-exposure group, with BLLs under 10 µg/dL, served as the control group. The heat-recovery rate of erythrocyte ALAD in this group was over 80%, which was similar to rates seen in people who did not have obvious lead exposure. BLL, smoking, and body-mass index were statistically significant predictors of change in finger blood flow with postural change (Ishida et al. 1996).

Examination of 60 workers in a lead-battery factory (Kovala et al. 1997) with quantitative electroencephalography (EEG) found that alpha (8-13/sec) and beta (14-40/sec) frequencies were more abundant in workers who had higher long-term lead exposure as measured by tibia lead (mean 26 µg/g), calcaneus lead (mean 88 µg/g), CBLI (mean 546 µg-years/dL), and time-weighted average BLL (mean 32 µg/dL). The finding of slow alpha activity correlated positively with lead exposure may reflect increased episodes of "microdrowsiness" in

workers who had higher lead exposure. In Niu's study (2000), quantitative EEG in 44 lead-exposed workers (mean BLL 29 µg/dL) found statistically significant increased beta activity and diminished amplitudes abnormalities in 81% of exposed workers compared with referents.

Essential Tremor

Essential tremor is a common neurologic disease with a prevalence in the general population of 1-6%. Prevalence is 4% in those over 40 years old and increases to 20.5% in those over 60 years old. The abnormal movement is related to involvement of the cerebellum and basal ganglia (Louis et al. 2003).

Louis et al. (2003) examined the relationship between BLL and essential tremor in 100 cases from a medical center in New York City (mean BLL 3.3 µg/dL) and 143 controls (mean BLL 2.6 µg/dL). Logistic regression adjusting for age and current cigarette-smoking found an association between BLL and essential tremor (OR per unit increase = 1.19; 95% CI: 1.03, 1.37; p = 0.02). BLL was higher in the 39 essential-tremor cases that had no family history. Both current prevalence and lifetime prevalence of occupational lead exposure were the same in essential-tremor cases and controls.

A second publication (Louis et al. 2005) examined whether an interaction between BLL and *ALAD* gene polymorphisms increases the odds of essential tremor. The study involved 63 essential-tremor cases that had a mean BLL of 3.5 µg/dL and 101 controls (similar in age, education, sex, and ethnicity) that had a mean BLL of 2.6 µg/dL. Of the 63 essential-tremor cases, 18 (29%) vs 17 (17%) of the controls had an $ALAD^2$ allele (OR = 1.98; 95% CI: 0.93, 4.21; p = 0.077). When log BLL was examined according to the presence of $ALAD^2$ allele in subjects who had essential tremor, log BLL was highest in cases that had an $ALAD^2$ allele, intermediate in cases that did not, and lowest in controls (test for trend, $\beta = 0.10$; p = 0.001). When the $ALAD^2$ allele was present, BLL was significantly associated with the odds of essential tremor (OR = 80.29; 95% CI: 3.08, 2.096; p = 0.008). The odds of essential tremor in people who had the $ALAD^2$ allele were 30 times greater than in those who had only the $ALAD^1$ allele. In the highest log BLL tertile, $ALAD^2$ allele was present in 22% of essential-tremor cases and 5% of controls. It was proposed that increased BLL with the $ALAD^2$ allele could affect the cerebellum and thereby increase the risk of tremor.

A similar study design was used in Mersin, Turkey, where 105 cases of essential tremor (mean age 52.9 ± 18.6 y) were compared with 69 spouse controls (mean age 50.9 ± 12.5 y) and 36 nonspouse controls (mean age 50.3 ± 15.9 y) (Dogu et al. 2007). Median BLL was 2.7 µg/dL in essential-tremor cases and 1.5 µg/dL in controls ($p < 0.001$). Logistic regression for BLL associated with essential tremor had an OR of 4.01 (95% CI: 2.53, 6.37; $p < 0.001$). Therefore, for each 1-µg/dL increase in BLL, there was a four-fold increase in the odds of essential tremor. The OR increased to 8.13 (95% CI: 3.05, 21.65; $p < 0.001$) when

the comparison was limited to nonspouse controls. This study replicated studies performed in New York City.

Another study by Louis et al. (2011) examined the interaction of harmane, a tremor-producing β-carboline alkaloid, and BLL in 106 cases of essential tremor (mean age 68.2 ± 15.2 y; median BLL 2.7 µg/dL, range 0.3-11.6 µg/dL) and 151 controls (mean age 64.1 ± 12.5 y; median BLL 2.4 µg/dL, range 0.3-11.9 µg/dL). Severity of tremor ranged from a score of 0 to 36. Tremor score correlated significantly with blood harmane concentrations and with BLL. The tremor score was low (8.4 ± 8.2) when both BLL and blood harmane were low, intermediate (10.5 ± 9.8) when one or the other was high, and highest (13.7 ± 10.4; $p = 0.01$) when both were high; this suggested an additive effect of exposure to the two toxicants.

Three of the four studies above were performed in New York City, and their case and control subjects overlapped. Therefore, the overall sample size in four studies at two locations may be only about 250. If low BLL is causally associated with the development of essential tremor, a much higher prevalence than 1-6% in the general population would be expected. Prospective studies of incident cases of essential tremor with measures of cumulative lead exposure are needed.

Summary Findings on Neurologic Effects

The committee concludes that the evidence is sufficient to infer causal relationships between BLLs under 40 µg/dL and adverse effects on nervous system function (see Table 4-1). Effects on both the central and peripheral nervous systems have been observed, including effects on cognitive function, peripheral nerve function, visual and auditory function, posture and balance, and autonomic nervous system function.

Neurobehavioral performance showed decrements in various domains in neurobehavioral testing, including verbal and visual memory, visuospatial ability, motor and psychomotor speed, manual dexterity, attention, and executive functioning associated with BLLs and measures of cumulative exposure (CBLI and bone lead levels). The committee focused on occupational studies, which it judged to be most relevant to the firing range. It found that decrements in neurobehavioral performance begin to occur at BLLs as low as 18 µg/dL. It also found that changes in mood were equivocal at BLLs of around 27-30 µg/dL, but lead-related symptoms could be detected at BLLs as low as 12 µg/dL despite the finding of some studies that there was no association with lead-related symptoms at BLLs over 30 µg/dL. Occupational lead exposure is associated with decrements in peripheral sensory nerve function beginning at BLLs around 28-30 µg/dL. BLLs over 10 µg/dL are associated with lead-induced hearing loss that

TABLE 4-1 Key Studies of the Effects of Lead on Neurologic Outcomes

Health Effect	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
Cognitive Performance					
Neuropsychologic test battery in English or French; 14 neuropsychologic variables examined by MANCOVA	467 Canadian former, current lead-smelter workers, French- and English-speaking; mean (SD) age = 43 (11.0) y; mean (SD) education = 10 (3.2) y	Mean (SD) BLL = 28 (8.4) µg/dL; mean (SD) employment = 18 (7.4) y; mean (range) time-weighted average BLL = 40 (4-66) µg/dL; mean (range) CBLI = 765 (1-1,626) µg-y/dL	MANCOVA (high, medium, low exposure); no significance with covariates (age, education, CES-D, alcohol use) until years of employment added suppressor variable; CBLI exposure groups differed significantly on some tests: digit symbol ($p = 0.05$), logical memory ($p = 0.04$), Purdue dominant hand ($p = 0.01$), Trails A ($p = 0.02$), Trails B ($p = 0.04$).	Study showed dose-effect relationship between CBLI and neuropsychologic performance when there was no association with current BLL.	Lindgren et al. 1996
Simple reaction time	80 currently employed smelter workers (from Lindgren cohort above); mean age = 44 y; mean (range) employment duration = 20 (1-26) y	Mean (SD) BLL = 26 (7.23) µg/dL; mean (SD) employment = 20 (5.6) y; mean (SD) tibia lead = 40 (25.17) µg/g bone mineral	Linear regression found BLL ± BLL^2 accounted for 13.7% of variance after adjustment for age, education ($p < 0.01$). Bone lead was nonsignificant. Curvilinear relationship found between BLL and SRT with threshold for increasing SRT at BLL of 30 µg/dL.	Curvilinear relationship may explain why previous studies reported faster SRTs in groups with lead exposure.	Bleecker et al. 1997
Mini-Mental State Examination (MMSE), reading section of Wide Range Achievement Test-revised (WRAT-R)	256 lead-smelter workers: mean (SD) age = 41 (7.9) y; mean (SD) education = 10 (2.8) y; mean (SD) employment duration = 17 (8.1) y	Current mean (SD) BLL = 28 (8.8) µg/dL; mean (SD) CBLI = 725 (434) µg-y/dL	Multiple linear regression adjusting for age, WRAT-R, education, alcohol, smoking found significant CBLI × WRAT-R interaction ($p = 0.01$) and dose-effect relationship	Greater cognitive reserve, as measured by educational achievement, allowed some compensation for effects of lead on neurobehavioral	Bleecker et al. 2002

(Continued)

TABLE 4-1 Continued

Health Effect	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
			between CBLI and MMSE ($p = 0.04$), but only in 78 workers with WRAT-R reading grade level below 6 y. Overall, most workers had reading grade equivalent to or below their years of formal education.	measures. Because most military personnel have demonstrated greater educational achievement and probably have greater cognitive reserve, they might have less effect of lead exposure.	
Verbal learning, memory: Rey Auditory Verbal Learning Test (RAVLT)	256 smelter workers currently employed who took test battery in English; mean (SD) age = 41 (7.9) y; mean (SD) education = 10 (2.8) y	Mean (SD) BLL = 28 (8.8) µg/dL; mean (SD) time-weighted average BLL = 39 (12.3) µg/dL; mean (SD) CBLI = 725 (434) µg-y/dL	Adjusting for age and WRAT-R compared lead exposure across three verbal memory groups based on encoding, storage, retrieval. BLL showed no difference, but time-weighted average BLL, CBLI were significantly higher in Group 3 (generalized memory impairment) than in Group 1 (no impairment) ($p < 0.05$ for both).	Cumulative lead exposure resulted in poorer storage and retrieval of previously learned material on verbal memory test.	Bleecker et al. 2005a
Neuropsychologic tests	54 lead-battery workers: Group 1 (n = 26), BLL never >50 µg/dL; mean (SD) age = 42 (9.3) y; Group 2 (n = 28): higher BLL in past, mean (SD) age = 47 (6.2) y; recent exposures reported as low	Group 1: mean CBLI = 330 µg-y/dL; maximum BLL = 40 µg/dL; time-weighted average BLL = 29 µg/dL; tibia lead = 20 µg/g; calcaneus lead = 79 µg/g	Low-exposure group showed decrements in visuospatial and visuomotor function (block design, memory for design, Santa Ana dexterity), attention (digit symbol, digit span), verbal comprehension (similarities) associated with	Average long-term exposures <40 µg/dL appeared to be related to decrements in visuospatial and visuomotor function. History of BLLs (CBLI) was better predictor of performance than bone	Hanninen et al. 1998

		Group 2: mean CBLI = 823 µg-y/dL; maximum BLL = 69 µg/dL; time-weighted average BLL = 40 µg/dL; tibia lead = 35 µg/g; calcaneus lead = 100 µg/g; CBLI, time-weighted average BLL, maximum BLL were also calculated for previous 3 y with median time-weighted average BLL (3 y) of 29 µg/dL	exposure to lead; increased reports of subjective symptoms. High-exposure group performed worse on tests. No correlation with bone lead. Study unable to determine lowest BLL that caused hazard to central nervous system function. In Group 1, those with median time-weighted average BLL (3 y) of 29 µg/dL had lower scores on visuospatial and visuoperceptive tasks. Average score was estimated to reflect maximum BLL of about 31 µg/dL.	lead levels. Results similar to Lindegren et al. (1996) study of CBLI that reflected past high exposure to lead that persisted after years of lower BLL. Bone lead did not reflect change in brain performance measures as well as CBLI.	
Modified version of World Health Organization Neurobehavioral Core Test Battery	803 lead-exposed workers (recruited from 26 lead-using facilities), 135 unexposed controls in South Korea	Lead exposed workers: mean BLL = 32 µg/dL; mean tibia lead = 37.1 µg/g; mean chelateable lead = 185.7 µg Controls: mean BLL = 5.3 µg/dL; mean tibia lead = 5.8 µg/g; mean chelateable lead = NA	Tibia lead level was not associated with neurobehavioral test scores.	Increase in BLL of 5 µg/dL was equivalent in its effects on test scores to increase of 1.05 y in age.	Schwartz et al. 2001
Neurobehavioral tests	576 of above lead workers in South Korea (Schwartz et al. 2001) who had completed 3 visits at 1-y intervals; mean (SD) age at baseline = 41 (9.5) y; mean (SD) job duration = 9 (6.3) y; 76% were men	Baseline mean (SD) BLL = 31 (14.2) µg/dL; mean (SD) tibia lead = 38 (43) µg/g	Various models demonstrated declines in test scores (executive abilities, manual dexterity, neuropsychiatric, peripheral nervous system sensory function) with historical tibia lead, longitudinal BLLs, cross-sectional (short-term)	Declines in neurobehavioral test scores were noted for long-term BLLs <40 µg/dL.	Schwartz et al. 2005

(Continued)

TABLE 4-1 Continued

Health Effect	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
			BLLs. Decrements in some tests noted when BLL increased from 21 µg/dL to 40 µg/dL. Increases in bone lead from 14 µg/g to 47 µg/g was associated with 2% lower test scores.		
MRI of brain	61 lead-smelter workers younger than 50 used in analyses because of large effect of age on outcome; mean (SD) age = 39 (8.8) y; mean (SD) education = 9 (2.8) y; mean (SD) employment duration = 19 (5.7) y; covariates drinking, smoking, hypertension, cholesterol, triglycerides, C-reactive protein	Mean (SD) BLL = 29 (6.89) µg/dL; mean (SD) CBLI = 826 (304.7) µg-y/dL; mean (SD) tibia lead = 39 (24.4) µg/g	WMC graded on MRI. Psychomotor speed and dexterity measured with GP. CBLI, bone lead were significantly higher in workers with WMC on MRI compared with those with no WMC. GP performance was significantly slower in WMC group and correlated significantly with CBLI, bone lead. Final regression models showed significant effect of CBLI, bone lead, WMC on GP after accounting for other cerebrovascular risk factors. Path diagram showed direct effect of lead exposure on GP that was mediated by indirect effect of WMC.	Cumulative past lead exposure associated with WMC. WMC mediated effect of lead exposure on psychomotor speed and dexterity in workers 50 y old or younger.	Bleecker et. al. 2007
MRS imaging data, brain *N*-acetyl aspartate (NAA), choline (Cho), total creatinine (tCr)	Case-control study of 22 workers in lead-paint factory, 18 factory workers that did not use lead; year not stated; 72-77% male;	Exposed workers: mean (SD) BLL = 16.99 (10.38) µg/dL; mean (SD) tibia lead = 61.55 (30.21) µg/g; mean	Blood and bone lead levels had significantly negative correlation with NAA:tCr, Cho:tCr ratios in frontal, occipital lobes compatible	Current and past lead exposures (bone lead) were associated with altered brain metabolism. Neuronal and axonal	Hsieh et al. 2009

	exposed workers' mean (SD) age = 45.7 (11.72) y; referents' mean (SD) age = 46.0 (10.14) y	(SD) patella lead = 66.29 (19.48) µg/g Referents: mean (SD) BLL = 3.4 (1.1) µg/dL; mean (SD) tibia lead = 18.5 (22.4) µg/g; mean (SD) patella lead = 7.14 (9.81) µg/g	with neuronal, axonal loss. Strongest regression coefficient was -0.023 (SE = 0.005, $p < 0.001$) for NAA:tCr ratio of frontal gray matter.	loss in frontal and occipital lobes agrees with findings in lead-exposed population of poorer performance on tests of visuospatial and visuomotor domain and executive function.	
Peripheral Neuropathy					
Sensory nerve conduction: CPT assessed large myelinated (CPT_{2000}), small myelinated (CPT_{250}), unmyelinated (CPT_5) sensory nerve fibers	74 primary lead-smelter workers; mean (SD) age = 44 (8) y; CPT in hand measured minimum transcutaneous current intensity needed to excite nerve fibers that were large myelinated, small myelinated, or unmyelinated	Mean (SD) BLL = 26 (7.1) µg/dL; mean (SD) bone lead = 40 (23.8) µg/g; mean (SD) CBLI = 891 (298.8) µg-y/dL. CBLI metrics of CBLI 20, CBLI 30, CBLI 40, CBLI 50, CBLI 60 as measure of CBLI above criterion BLLs of 20, 30, 40, 50, and 60 µg/dL, respectively.	CPT had significant curviline ar relationship with time-weighted average BLL, with minimum at 28 µg/dL ($p < 0.03$). Unique variance of CPT explained by CBLI metrics with increasing criterion BLLs found increasing variance from CBLI 20 ($R^2 = 5.8\%$, $p < 0.03$) to CBLI 60 ($R^2 = 23.3\%$, $p < 0.005$). Significant interaction between CBLI 60 and measure of ergonomic stess of upper extremities was found ($R^2 = 6.1\%$, $p < 0.02$).	Measures of chronic blood lead exposure associated with impairment of large and small myelinated sensory nerve fibers. Effect enhanced at highest doses by ergonomic stressors. Effects may occur with average BLLs as low as 28 µg/dL.	Bleecker et al. 2005b
Vibration perception measured in hand, foot	206 lead-battery workers in Taiwan; mean age = 41 y	Annual BLL for previous 5 y; current mean BLL = 28 µg/dL; mean BLL over previous 5 y = 32 µg/dL; mean maximum BLL = 39 µg/dL; mean index of cumulative exposure = 425 µg-y/dL; mean	Significant association ($p < 0.05$) between mean BLL and mean time-weighted index of cumulative exposure and vibration perception in foot was found after adjustment for age, sex, height, smoking, alcohol consumption, use of vibrating hand tools. After adjustment for	Decrease in vibration threshold, with possible threshold around 30 µg/dL.	Chuang et al. 2000

(Continued)

TABLE 4-1 Continued

Health Effect	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
		time-weighted index of cumulative exposure = 32 µg/dL; mean working duration = 13 y; percentage of lifespan in work at plant 31%	covariates, hockey-stick regression analysis of foot vibration threshold vs mean BLL for 5 y found inflection point around 30 µg/dL. Positive linear relationship above this point suggested possible threshold.		
Nerve conduction studies, vibration thresholds, quantitative EEG	60 workers in lead-battery factory; mean (SD) age = 43 (9) y; mean (SD) exposure duration = 16 (8) y	Mean (SD) tibia lead = 26 (17) µg/g; mean (SD) calcaneus lead = 88 (54) µg/g; mean (SD) CBLI = 546 (399) µg-y/dL; mean (SD) time-weighted average BLL = 34 (8.4) µg/dL; mean (SD) maximum BLL = 53 (19) µg/dL; mean (SD) BLL = 27 (8.4) µg/dL.	Nerve conduction had negative correlation with CBLI, duration of exposure that was unrelated to age. Vibration threshold at ankle related significantly to CBLI ($p < 0.05$), duration of exposure ($p < 0.1$) after adjustment for age. Vibration threshold in finger was associated with BLL (26 µg/dL) and BLL averages over preceding 3 y (29 µg/dL). Alpha and beta frequencies found more frequently in workers with higher, long-term lead exposure. Overall, historical BLLs more closely associated with peripheral nerve function than bone lead concentrations. No comparison group; no consideration of effect of smoking, alcohol use in this population.	Study suggests negative effects on peripheral nervous system at average BLLs <30 µg/dL.	Kovala et al. 1997

Sensory Organs					
BAEP	359 English- and French-speaking, currently exposed male lead-smelter workers; mean (SD) age = 41 (9.0) y; mean (SD) employment duration = 17 (7.9) y	Mean (SD) BLL = 28 (8.4) µg/dL; mean (SD) time-weighted average BLL = 39 (11.9) µg/dL; mean (SD) CBLI = 719 (421.0) µg-y/dL	Partial correlation analyses adjusting for age found BLL, time-weighted average BLL significantly associated with wave I latency ($r^2 = 0.13$, $p < 0.01$ and $r^2 = 0.11$, $p < 0.05$, respectively), and CBLI significantly associated with wave III latency ($r^2 = 0.16$, $p < 0.01$). In regression model of full group after adjustment for age, BLL and time-weighted average BLL accounted for significant variance of wave I (change in $r^2 = 1.8\%$, $p < 0.01$ and change in $r^2 = 1.2\%$, $p < 0.05$, respectively); CBLI accounted for significant variance of wave III latency (change in $r^2 = 2.8\%$, $p \leq 0.00$), and I-III interpeak interval (change in $r^2 = 1.4\%$, $p < 0.03$).	Lead exposure interferes with brainstem auditory evoked potentials in dose-dependent manner.	Bleecker et al. 2003
Hearing loss; audiometric examination of hearing thresholds	412 steel-plant workers	BLL (and other metals); noise levels in different working zones	Lead was only metal in blood found significantly correlated with hearing loss for most tested sound frequencies ($p < 0.05$ to $p < 0.0001$). After adjustment for age, noise level, logistic regression model	BLLs below 10 µg/dL might enhance noise-induced hearing loss.	Hwang et al. 2009

(Continued)

TABLE 4-1 Continued

Health Effect	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
			analysis indicated that BLL >7 µg/dL was significantly associated with hearing loss at sound frequencies of 3,000-8,000 Hz with ORs of 3.06-6.26 ($p < 0.05 \sim p < 0.005$).		
Hearing loss; audiometric examination: hearing thresholds for 6 frequencies, method for calculating average hearing threshold	Cases: 121 male workers in outpatient occupational-health clinic with average hearing loss of 25 dB; Controls: 121 workers for occupational health examinations with normal hearing thresholds (<25 dB); Average age = 39.4 $\pm$ 9.8 y	Concurrent BLL: cases, 10.7 µg/dL; controls, 3.9 µg/dL; arsenic, selenium, manganese also measured	Multiple regression found lead, age had negative effect on hearing, selenium had positive (protective) effect. Net effect of lead: 7.11 dB when logarithmically transformed lead level is increased by 0.1 µg/dL. Years exposed to work related to noise affected hearing ability weakly, not significantly.	Lead exposure associated with hearing loss.	Chuang et al. 2007
Postural balance; postural sway measures with spectral analysis	121 lead workers, 60 unexposed controls	BLLs 6-89 (mean = 40) µg/dL	BMDLs of BLL (lower 95% confidence limits of BMD) were estimated to be 12.1-17.3 (mean = 14.4) µg/dL for postural sway. All postural sway measures except sagittal sway with eyes open were significantly larger in lead workers than controls ($p \leq 0.001$).	BLLs as low as 14 µg/dL may affect postural balance and stability.	Iwata et al. 2005
Vision, prolonged visual evoked potentials	300 men; 30-40 y old	BLL = 17-60 µg/dL	Correlation between BLL and increased latencies of visual evoked potentials starting at 17-20 µg/dL.	Lead can affect speed of conduction in nerves controlling vision at BLLs <20 µg/dL.	Abbate et al. 1995

Cardiac autonomic (parasympathetic) nervous system function; respiratory variation in heart rate (R-R interval) measured in ECG recordings (12 standard leads) in supine position during normal, deep breathing	Cross-sectional survey of 172 male workers in lead storage-battery factories, lead refineries; mean exposure = 6.6 y (0.1-26.3 y); analysis of subgroup of 132 workers with exposure to lead for more than 1 y	Mean BLL = 36 µg/dL (5-76 µg/dL)	For 132 workers exposed to lead for more than 1 y who had relatively stable BLLs (variation less than 20 µg/dL during preceding year), significant ($p < 0.01$) dose-related decrease in cardiac parasympathetic function was observed. Decrease in CV, % CV of R-R interval during deep breathing indicated that effects on cardiac parasympathetic activity occurred at BLLs of ≥30 µg/dL; mild decrease possibly occurred at ≥20 µg/dL.	Effect in younger groups was more obvious than that in older groups, suggesting that lead's effect on cardiac parasympathetic function is greater in younger populations and is modified by aging.	Teruya et al. 1991

Abbreviations: BAEP, brainstem auditory evoked potential; BLL, blood lead level; BMD, benchmark dose; BMDL, benchmark dose level; CBLI, cumulative blood lead index; CES-D, Center for Epidemiological Studies-Depression Scale; CPT, current perception threshold; CV, coefficient of variation; ECG, electrocardiogram; EEG, electroencephalogram; GP, grooved pegboard; MANCOVA, multivariate analysis of covariance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; OR, odds ratio; SD, standard deviation; SE, standard error; SRT, simple reaction time; WMC, white matter change; WRAT-R, wide range achievement test-revised.

might enhance noise-induced hearing loss. BLLs of 17-20 µg/dL are associated with a decrease in conduction velocity in the visual pathway. The benchmark dose level of the BLL for postural sway is 14 µg/dL. Parasympathetic and sympathetic integrity is compromised in lead-exposed workers who have mean BLLs over 20 µg/dL. Quantitative EEG found increased beta activity in 81% of lead-exposed workers whose mean BLL was 29 µg/dL.

The committee also notes that cumulative lead dose that reflects past high lead exposure may be a strong predictor of decrements in neurobehavioral performance even in the absence of an association with current BLL. Cognitive effects of lead exposure may be present years after cessation of occupational lead exposure in older adults. Those finding are in general agreement with NTP and EPA reports.

HEMATOPOIETIC EFFECTS

Environmental and occupational lead poisonings have long been associated with anemia, whose mechanisms are complex and multifactorial. A review by Aub et al. (1925) concluded that severe lead poisoning was associated with anemia that was initially due to enhanced destruction of circulating erythrocytes followed by "bone marrow failure". Those and other aspects of the anemia of lead poisoning have been well documented, and their mechanisms are now better understood. Exposure to lead has been associated with changes in erythrocyte structure and decreases in hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin concentration. This section will briefly review three aspects of the anemia of lead poisoning: shortened erythrocyte survival, impaired heme synthesis, and impaired renal production of erythropoietin. It will then provide estimates of the BLLs at which those phenomena occur.

Conclusions from the 2012 Environmental Protection Agency and 2012 National Toxicology Program Lead Documents

Environmental Protection Agency 2012 Integrated Science Assessment for Lead (Second External Review Draft)

EPA's review of recent epidemiologic studies concerning environmental lead exposure and hematologic function concludes that there is strong evidence that exposure is associated with a variety of deleterious effects on hemoglobin concentration, mean corpuscular volume, mean corpuscular hemoglobin, and erythrocyte count and adverse effects on heme synthesis through the inhibition of several enzymes of the heme pathway. EPA's draft report concludes that deleterious associations are observed in populations that have mean BLLs as low as about 5 µg/dL.

National Toxicology Program 2012 Monograph on Effects of Low-Level Lead

The NTP monograph did not consider effects of lead exposure on hematologic functioning.

Other Studies Considered

Erythrocyte Survival and Anemia

The use of radiolabeling techniques to measure erythrocyte survival times in men who worked in battery and lead-smelting plants and were heavily exposed to lead revealed that erythrocyte survival was shortened from a mean of 120 days in nonexposed men to 101 days in 17 workers, three of whom were symptomatic (Hernberg et al. 1967). BLLs were not measured in that landmark study, and the diagnosis of lead poisoning was made by measuring increased coproporphyrin in urine (over 500 µg/L). Heightened osmotic fragility and changes in erythrocyte shapes have long been thought to be responsible for the enhanced erythrocyte destruction; indeed, in experimental animals, removal of the spleen, the organ responsible for erythrocyte sequestration, temporarily reverses the anemia of lead poisoning (Aub et al. 1925).

Several reports of occupational lead poisoning from the 1970s suggested that a decrease in hemoglobin concentrations occurred only when the BLL reached about 50 µg/dL (Lilis et al. 1978; Baker et al. 1979; Grandjean 1979). However, more recent research indicates that effects may occur at substantially lower exposure. For example, in an attempt to establish the benchmark dose of lead that is associated with anemia in the workplace in Japan, 388 male lead-exposed workers in a variety of industries were examined for BLL, erythrocyte counts, hemoglobin, and hematocrit. BLLs ranged from 1.0 to 113.3 µg/dL (mean 26.8 µg/dL). After controlling for age and working status, BLL was statistically significantly associated with small decrements in hemoglobin concentration, erythrocyte counts, and hematocrit. The benchmark BLLs "at an abnormal probability of 5% in unexposed workers and an excess risk of 5% in exposed workers" were estimated with the method of Budtz-Jorgensen et al. (2001) to be 19.5 µg/dL for hemoglobin, 19.4 µg/dL for erythrocytes, and 29.6 µg/dL for hematocrit (Karita et al. 2005, p. 957).

Measurements of bone lead and hemoglobin in 119 union members involved in the building trades have also been revealing. Patella lead concentrations were found to correlate significantly with a small decrease in hemoglobin and hematocrit; in the same men, BLLs were relatively low (mean 8.3 µg/dL) and were not associated with these outcomes (Hu et al. 1994). Those seemingly disparate findings suggest a subclinical effect of bone lead burden on erythro-

poiesis despite relatively low concurrent BLLs. A recent study of 15 exposed workers (mean BLL 74 μg/dL) and 15 nonexposed workers (mean BLL 9.9 μg/dL) found that the exposed workers had more than twice the erythrocyte intracellular calcium levels of nonexposed workers and that high intracellular calcium concentration was associated with increased osmotic fragility. In the same workers, lead exposure was associated with increased erythrocyte membrane lipid peroxidation as estimated with measurements of erythrocyte malondialdehyde (Quintanar-Escorza et al. 2007). Another recent study of 23 battery workers (mean BLL 50 μg/dL; range 5-90 μg/dL) and 36 controls (mean BLL 1.5 μg/dL) found an increase in several erythrocyte markers of oxidative damage but no change in hematologic measures (Conterato et al. in press). Several more recent studies have also suggested effects of lead on hematopoiesis at relatively low BLLs. A Nigerian study of 81 men moderately exposed to lead in manufacturing occupations reported a decrease in hemoglobin and increased circulating reticulocytes in men who had a mean BLL of only 7 μg/dL compared with controls (mean BLL 3 μg/dL) (Ukaejiofo et al. 2009), but nutritional and other risk factors for reduced hemoglobin were not discussed. Finally, a study in Sarajevo examined hematologic outcomes in a population of workers in the petrol industry whose mean BLL was 4.3 μg/dL. Associations were found between BLL and erythrocyte counts, hemoglobin concentrations, and mean corpuscular volume (Cabaravdic et al. 2010); however, exposures to other toxic chemicals cannot be ruled out.

Collectively, the large body of research on lead and anemia, only briefly explored here, consistently indicates that occupational exposure to lead is associated with biochemical and morphologic damage of erythrocytes. Moreover, the notion that BLLs over 50 μg/dL are required appears to have been put to rest by more recent research.

Impaired Heme Synthesis

The consequences of lead exposure for the biosynthesis of heme have been studied for decades; at times, various intermediates in the heme synthetic pathway have been used as biomarkers of exposure and effect. Indeed, in 1993, a National Research Council committee issued a report Measuring Lead Exposure in Infants, Children, and Other Sensitive Populations that reviewed the literature on lead and the heme biosynthetic pathway in a chapter titled "Biologic Markers of Lead Toxicity" (NRC 1993). The reader is referred to that chapter for a full description of the issue. A brief summary and interpretation of this large body of research are presented below.

The first step in the heme pathway takes place inside mitochondria and involves the enzymatic condensation of succinyl-CoA with glycine to form delta-aminolevulinic acid (ALA) via the enzyme ALA-synthase (Figure 4-1). That is

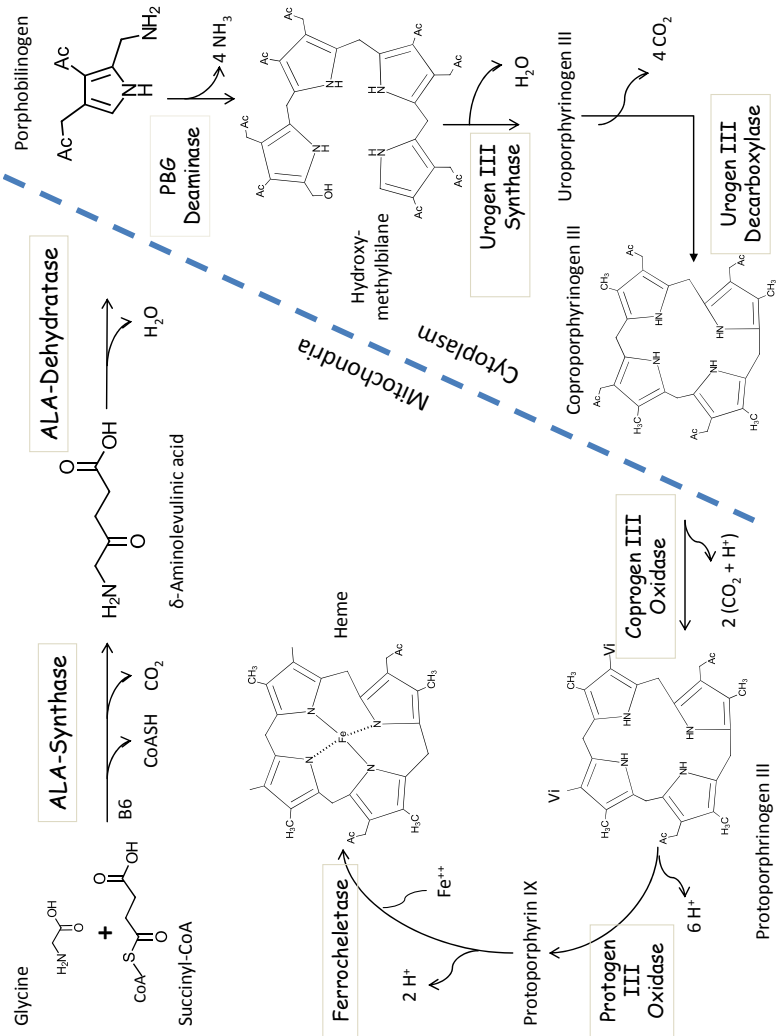

FIGURE 4-1 The biosynthetic pathway of heme.

also the rate-limiting step in heme synthesis. The second step involves the lead-sensitive enzyme ALAD, which combines two molecules of ALA to form porphobilinogen. Four molecules of porphobilinogen are enzymatically joined in the cytosol to form the first of a series of porphyrin molecules, including uroporphyrinogen, which is excreted in urine; coproporphyrinogen, which is excreted in urine and feces; protoporphyrinogen; and finally protoporphyrin IX, the precursor of heme. The final step in the synthesis of heme involves the insertion of an iron atom into protoporphyrin IX via the enzyme ferrochelatase, another lead-sensitive enzyme.

As early as 1947, the urinary excretion of porphyrins in urine was described as "the first symptom of lead poisoning" due to the inhibition of heme synthesis by lead (de Langen and ten Berg 1948). It is now known that other health effects precede the excretion of porphyrins in urine, which typically does not occur until BLLs exceed 40 µg/dL. Historically, other intermediates of heme synthesis have been used as diagnostic markers of occupational and environmental lead poisoning. Hernberg and Nikkanen (1970) published landmark findings in an urban population that the zinc metalloenzyme ALAD is exquisitely sensitive to lead, with 50% enzyme inhibition occurring at BLLs over 15 µg/dL. Measured erythrocyte ALAD or urinary ALA was later widely used as a lead biomarker. Several years later, Piomelli et al. (1973) developed the "FEP test" (free erythrocyte porphyrin test) as a screening test for childhood lead poisoning. Renamed as the ZPP test (zinc protoporphyrin test), this test took advantage of the fact that the partial inhibition of the final step in heme synthesis led to the accumulation of protoporphyin IX, a fluorescent biomarker that is easily detectable in a fingerstick blood sample. Widely used for many years, the test fell by the wayside in 1991 when the Centers for Disease Control (now the Centers for Disease Control and Prevention) lowered the BLL of concern to 10 µg/dL; a BLL of at least 17 µg/dL is required before porphyrins are increased in blood (Piomelli et al. 1982).

Thus, it is clear that the impairment of heme synthesis by lead exposure occurs at relatively low BLLs and that increased concentrations of ALA and protoporphyrin are associated with lead exposure. However, it is not widely recognized that the inhibition of heme synthesis cannot fully explain the anemia of lead poisoning. The elegant work of Piomelli et al. (1975) has demonstrated that even in patients with BBLs over 90 µg/dL, erythrocytes contain roughly 300 molecules of heme for every molecule of free protoporphyrin. Thus, other molecular mechanisms must play more important roles in the etiology of the anemia.

Impaired Production of Erythropoietin

Grandjean et al. (1989) conducted a simple experiment that demonstrated that after donating a unit (450 mL) of blood, workers occupationally exposed to lead (mean BLL 44 µg/dL) took longer to restore their predonation hemoglobin

concentrations than a group of age-matched controls. Over the 4 weeks after blood donation, the workers' hemoglobin concentrations and reticulocyte counts dramatically lagged behind those of controls. The authors attributed the "delayed blood rejuvenation capacity" to impaired heme synthesis. But the work of Piomelli et al. (1975), described above, argues against that. Others have postulated that the failure to mount an adequate reticulocytosis to compensate for blood loss might be due to inadequate production of erythropoietin in the kidney, inasmuch as erythropoietin is produced by cells in the proximal tubule of the kidney, where lead is known to accumulate. Thus, Graziano et al. (1991) studied the relationships between BLL, hemoglobin concentration, and erythropoietin in a population of pregnant women in two towns in Kosovo (in the former Yugoslavia), one of which was the site of a lead smelter. It was demonstrated that lead-exposed women had inappropriately low circulating erythropoietin levels at any given level of hemoglobin. The relationship between BLL and erythropoietin was later described in lead workers in Austria (Osterode et al. 1999) and in a population of tricycle taxi drivers in Nepal (Sakata et al. 2007). Thus, the anemia associated with lead exposure may be partially due to lead nephrotoxicity and the failure to synthesize erythropoietin adequately to regulate erythropoiesis.

Summary Findings on Hematopoietic Effects

Occupational exposure to lead has consistently been associated with biochemical, morphologic, and physiologic effects that can impair erythrocyte formation and survival and ultimately lead to anemia. However, the literature varies in its estimates of the BLLs required to have clinically significant effects on those outcomes. Table 4- 2 summarizes the studies and presents the BLL associated with each particular hematologic outcome.

The committee concludes that the evidence is sufficient to infer causal relationships between BLLs under 40 µg/dL and effects on heme synthesis. The evidence is suggestive with regard to possible effects of BLLs on circulating hemoglobin concentrations at a benchmark dose of 20 µg/dL. There is also convincing evidence that higher BLLs are associated with delayed blood rejuvenation after blood loss—an issue of possible concern in a population of military personnel. Those conclusions are generally in agreement with the conclusions of EPA (2012); the NTP review did not address hematologic effects of lead.

RENAL EFFECTS

Adverse effects of lead exposure on renal function were first described in the 19th century (Lanceraux 1881). There is now a voluminous literature on the relationship between environmental and occupational lead exposure and renal function. It includes many epidemiologic studies and a broad array of mechanistic toxicology studies in animal models.

TABLE 4-2 Key Studies of the Hematopoietic Effects of Lead

Health Effect	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
Shortened erythrocyte survival	Battery and smelter workers (n = 17) and controls (n = 4)	Urinary coproporphyrin >500 µg/L	Erythrocyte survival was 101 days in workers vs 120 days in controls.	Clinically important outcome.	Hernberg et al. 1967
Anemia	Smelter workers and a chemicals plant (n = 160)	BLLs about ≥50 µg/dL	Anemia (Hgb <14 g/dL) seen in 21% of workers.	Clinically important outcome.	Baker et al. 1979
Decreased erythrocytes, HCT, and Hgb	Various industries in Japan	Estimated benchmark doses of about 20 µg/dL for hemoglobin, erythrocytes, about 30 µg/dL for HCT	Onsets of declines in these measures begin at these BLLs.	Facilitates risk assessment, management decisions.	Karita et al. 2005
Decreased Hgb and HCT with patella lead but not BLL	Men in building trades	Patella bone lead in men with mean BLL of 8.4 µg/dL	Compared with those in lowest quintile of bone lead, those in highest had decrease in Hgb, HCT of 11 g/L, 0.03, respectively.	Suggests effects at relatively low exposures in range of interest.	Hu et al. 1994
Increased erythrocyte calcium, fragility and lipid damage	Lead workers	Mean BLL >70 µg/dL	Erythrocyte calcium >2×, lipid peroxidation 1.7 × higher in lead workers than controls.	Suggests mechanism for shortened erythrocyte survival.	Quintanar-Escorza et al. 2007
Inhibition of erythrocyte ALAD activity	Urban population	No apparent BLL threshold	Negative correlation between BLL and ALAD activity; y = 2.3-0.18x; r = -0.83.	Early biochemical evidence of toxicity.	Hernberg and Nikkanen 1970
Inhibition of heme synthetase	Various	BLL threshold 17 µg/dL	Onset of rise in erythrocyte protoporphyrin begins at this BLL.	Basis of ZPP test; evidence of toxicity at BLLs that may occur on firing ranges.	Piomelli et al. 1973, 1982

Delayed blood rejuvenation capacity	Lead workers (n = 25) and age-matched controls (n = 25)	Mean BLL 44 µg/dL in workers	After donating blood, workers took roughly 2 weeks longer to return to predonation Hgb level.	Delayed capacity to respond to blood loss is important in military population.	Grandjean et al. 1989
Reduced serum erythropoietin at mid-pregnancy and delivery	Pregnant women in a smelter town and control town in Kosovo. For each stratum of Hgb, the sera of those with the highest and the lowest BLLs were selected for erythropoietin analysis.	Mean BLLs 2-4 µg/dL in lower BLL groups, 17-39 µg/dL in higher BLL groups	ANOVA treating BLL as discrete variable (high vs low) found significant BLL effect at midpregnancy ($p = 0.05$), delivery ($p = 0.009$).	Explains delayed blood rejuvenation.	Graziano et al. 1991

Abbreviations: ALAD, delta-aminolevulinic acid dehydratase; ANOVA, analysis of variance; BLL, blood lead level; Hgb, hemoglobin; HCT, hematocrit; ZPP, zinc protoporphyrin.

Conclusions from the 2012 Environmental Protection Agency and 2012 National Toxicology Program Lead Documents

Environmental Protection Agency 2012 Integrated Science Assessment for Lead (Second External Review Draft)

EPA's draft assessment concluded that recent and past basic toxicologic research and epidemiologic studies provided a strong body of evidence supporting the conclusion that nonoccupational lead exposure is causally associated with an increased risk of renal disease, as evidenced by increased serum creatinine, reduced creatinine clearance, and reduced glomerular filtration rate (GFR). EPA concluded that the evidence was sufficiently strong to support a causal relationship between lead exposure and renal disease, but the present committee judged that BLLs and duration of lead exposure at which the effects occur are uncertain because BLLs in adults probably reflect higher BLLs earlier in life.

National Toxicology Program 2012 Monograph on Effects of Low-Level Lead

Largely on the basis of a review of 13 large epidemiologic studies of the general population that examined associations between renal function and BLLs under 10 µg/dL, the NTP concluded that there was sufficient evidence that BLLs under 5 µg/dL are associated with adverse effects on renal function in adults. The 13 studies support relationships between concurrent BLL and renal function. The associations are typically stronger in susceptible populations (such as people who have diabetes or hypertension). However, the NTP report concluded that concurrent BLLs in adults may reflect higher BLLs in childhood or earlier adulthood. In the absence of a study of a population in which BLLs remained under 10 µg/dL for life, the effects of early vs late lead exposure on renal function cannot be discerned.

Other Studies Considered

Although the committee's review focused on epidemiologic evidence, it is important to note that decades of studies in animal models have provided compelling evidence of lead-induced histopathologic changes in renal structure, particularly proximal tubular damage and sclerosis. They have also provided a suite of plausible molecular mechanisms of renal damage, including lead-induced mitochondrial dysfunction, inflammation, oxidative stress, and apoptosis (EPA 2012). Thus, the epidemiologic findings of lead-induced renal impairment, discussed below, are supported by biologic plausibility.

Renal function is characterized by the glomerular filtration or active tubular pumping of wastes and the simultaneous retention of essential molecules, such as water, glucose, amino acids, and electrolytes. Various techniques are

used to assess GFR clinically, including the measurement of creatinine clearance or serum cystatin C, a protein produced by all nucleated cells that undergoes glomerular filtration and tubular reabsorption in the kidney (Fried 2009). However, the measurement of GFR is not helpful in predicting early stages of clinical dysfunction. Recent research has also used the measurement of early-effect biomarkers, such as urinary B2-microglobulin, which normally is reabsorbed in the proximal tubules, and *N*-acetyl-β-D-glucosaminidase (NAG), a tubular enzyme that appears in urine as a result of cell death. Those and other so-called early-effect markers have not yet been sufficiently validated as predictors of *clinical* renal disease in populations exposed to nephrotoxic chemicals, but they serve as early indicators of toxicity.

Epidemiologic studies of the relationship between lead exposure and renal function can be divided into three categories: studies of the general population, which experiences environmental exposure; studies of the contribution of lead to disease progression in those who have chronic kidney disease (CKD); and studies of occupationally exposed workers. The evidence from studies in the first two categories is overwhelmingly convincing that lead exposure plays a role in the onset and progression of renal dysfunction. Epidemiologic studies of occupationally exposed workers are somewhat less consistent, in large part because they involve small samples and consequently have very poor statistical power and are unable to statistically adjust adequately for important confounding factors. Occupational studies also suffer from the healthy-worker effect (workers tend to be healthier than the general population and have lower mortality and morbidity rates, which could mask adverse effects of harmful exposures), other kinds of selection bias, and other methodologic issues.

Studies of the General Population

Numerous studies of the general US population derived from several NHANES evaluations have described associations between BLLs and renal function. They and the Normative Aging Study (Kim et al. 1996; Tsaih et al. 2004) and the Swedish Women's Health Study (SWHS) (Åkesson et al. 2005) led NTP to conclude that "there is *sufficient* evidence available for an association between current [BLLs] <5 µg/dL in adults, measured at the time of study, and reduced kidney function in general populations" (NTP 2012, p. 102). For example, in an NHANES study of BLL and renal function in nearly 10,000 adults recruited in 1999-2002, Muntner et al. (2005) described an increased risk of CKD, defined as an estimated GFR under 60 mL/min/1.73 m^2. Compared with those in the lowest quartile of BLL (under 1.06 µg/dL), people in the highest quartile (over 2.47 µg/dL) were 2.72 (95% CI: 1.47, 5.04) times more likely to have CKD. In support, Navas-Acien et al. (2009), in a comparable study of nearly 15,000 adults evaluated during 1999-2006, observed reduced GFR in those who had BLLs over 2.4 µg/dL vs those who had BLLs of 1.1 µg/dL or lower (adjusted OR = 1.56; 95% CI: 1.17, 2.08). The latter study also observed a

small but statistically significant trend for albuminuria. It controlled for more covariates, including blood cadmium concentration and blood pressure. Comparable findings of an association of remarkably low BLL with reduced GFR had been described in the SWHS (Åkesson et al. 2005). To put the SWHS study findings into perspective with regard to other factors that influence renal function, it should be noted that EPA calculated that the magnitude of the impact of a change in BLL from 1.1 µg/dL (the SWHS 5th percentile) to 4.5 µg/dL (the 95th percentile) on GFR "would be comparable to the loss of renal function associated with an increase in [body mass index] of 7 kg/m^2 or an increase in age of 4.7 years" (EPA 2006, 2012).

For years, the idea of reverse causality (that impaired renal function results in reduced elimination of lead from blood and therefore a high BLL) could not be ruled out. Given the cross-sectional nature of the studies described above, it is not possible to rule it out on the basis of the studies alone. However, many earlier studies clearly suggested that renal dysfunction is caused by lead exposure (Batuman et al. 1981, 1983; Emmerson 1991). New lines of investigation also appear to rule out reverse causality. In Taiwan, in a 4-year longitudinal study of patients who had CKD, baseline BLL was associated with a decline in renal function (Yu et al. 2004). And in the Normative Aging Study, BLL and serum creatinine were associated even when serum creatinine was in the normal range (Kim et al. 1996; Tsaih et al. 2004). Thus, it does not appear that impaired renal function is required to drive the association between the two biologic measures.

At first glance, the very low BLLs associated with CKD in the NHANES and other large cross-sectional studies may appear to defy credibility. However, it is important to appreciate, as noted in Chapter 3, that BLL in adulthood probably captures cumulative dose to some extent.

Studies of Patients Who Have Chronic Kidney Disease

Several clinical studies of patients who have CKD have provided additional evidence of a causal relationship between lead exposure and a decline in renal function. In the above-mentioned longitudinal study in Taiwan, 121 patients who had well-controlled CKD were enrolled. One way to estimate the soft-tissue burden of lead is to administer a dose of calcium disodium ethylenediamine tetraacetic acid ($CaNa_2EDTA$), a lead-chelating agent, and measure the amount of chelatable lead excreted in urine during the ensuing 72 h. Both $CaNa_2EDTA$-chelatable lead and BLL at baseline were associated with statistically significant declines in serially measured GFR during the ensuing 4 years (Yu et al. 2004). Additional evidence was derived from a randomized clinical trial in 202 patients who had chronic renal insufficiency (serum creatinine 1.5-3.9 mg/dL). After a 24-month observation period, 64 patients who had increased $CaNa_2EDTA$-chelatable lead and a mean BLL of 5.3 µg/dL were randomized to receive either chelation therapy with intravenous $CaNa_2EDTA$ or intravenous

placebo and were followed for more than 2 years. During the first 3 months of the trial, there was a statistically significant improvement in those who received $CaNa_2EDTA$ chelation therapy but not in those who received placebo. In addition, the later rate of decline in GFR was lower in the chelated group than in the placebo group (Lin et al. 2003). It is possible, however, that the improvement in renal function was due to effects of $CaNa_2EDTA$ treatment other than lead removal, inasmuch as antioxidant effects and improved blood flow have also been described in connection with this drug (Jacobsen et al. 2001; Saxena and Flora 2004; EPA 2012). Nevertheless, collectively, those and other studies of patients who had renal impairment indicate a role of low-level lead exposure and progression of disease in patients who have diabetes (Lin et al. 2006a) and who do not have diabetes (Lin et al. 2006b; EPA 2012).

Studies of Occupational Exposures

Chronic lead nephropathy in the occupational setting has been noted for many years, but the lead dosimetry in early studies was generally poorly characterized (Emmerson 1973; Cramér et al. 1974; Wedeen et al. 1975). Most of the occupational studies have been small and have failed to consider other important confounders of the association between lead exposure and renal function adequately. In addition, the healthy-worker effect, which is probably pronounced in industries in which health surveillance is required, may bias possible associations toward the null (Ekong et al. 2006).

A longitudinal study of a large population of current and former workers in 26 lead-using facilities in South Korea has to some extent been able to overcome those limitations. Workers were evaluated three times, roughly a year apart, for BLL, tibia bone lead, and markers of renal function (Weaver et al. 2009). In the initial cross-sectional analysis of 803 lead workers (mean BLL 32 µg/dL; standard deviation 15) and 135 controls, it appeared that lead exposure in the "moderate dose range" was adversely associated with renal function (as measured by serum creatinine, creatinine clearance, and blood urea nitrogen), especially in older workers (Weaver et al. 2003).

At the third evaluation, 537 current and former workers, 25% of whom were women, were available for analysis (Weaver et al. 2009). Using various statistical methods, the investigators attempted to separate the effects of recent dose (BLL) from cumulative dose (tibia lead) by controlling for baseline BLL and tibia lead. That effort was complicated by the fact that mean BLL did not differ among evaluations 1-3 in either sex. Nevertheless, both current and cumulative lead dose were associated with changes in renal function. In reviewing that work, EPA (2012) pointed out that the problem with setting a threshold for BLL regarding kidney outcomes is related to differential responses according to age. In young workers, there is a hyperfiltration pattern in which GFR increases as BLL (or tibia lead) increases. The opposite pattern, indicative of "traditional nephrotoxicity", is observed in older workers.

An additional study of the Korean cohort has explored possible effect modification of the relationship between occupational lead exposure and renal function. A polymorphism of the vitamin D receptor (the variant B allele) was found to worsen the association between lead exposure and renal function. And in those who had the *ALAD*^{2} allele, higher BLLs were associated with higher calculated creatinine clearance (Weaver et al. 2006).

Several other studies published in the last 5 years have reported adverse associations between occupational lead exposure and impaired renal function. A study in Nigeria described impaired creatinine clearance in 190 lead workers (mean BLL 50 µg/dL) compared with 80 controls but did not adjust for any covariates (Alasia et al. 2010). A study of 87 industrial workers (mean BLL 29 µg/dL) and 61 controls in Pakistan reported statistically significant correlations between BLL and serum creatinine, uric acid, and several early biologic markers of renal dysfunction (Khan et al. 2008). Early biologic markers of tubular and glomerular function were explored in 155 battery workers (mean BLL 20 µg/dL) and 36 controls in China (Sun et al. 2008). The study reported a dose-response relationship between BLL and renal function, biomarkers of bone metabolism, and the prevalence of osteoporosis. Those and many other studies summarized by EPA (2012) have been rather consistent in making the link between occupational lead exposure and impaired renal function.

Studies of Renal Endocrine Function

In addition to its primary role as an excretory organ, the kidney has some endocrine functions, including the synthesis of the hormone erythropoietin (EPO) in the specialized epithelial-like cells in the peritubular capillary lining of the renal cortex and the synthesis, in the juxtaglomerular apparatus of the kidney, of renin, an enzyme that is intimately involved in the regulation of blood pressure via the renin-angiotensin-aldosterone system. EPO is responsible for the stimulation of erythropoiesis in the bone marrow and plays a role in preventing neuronal death after cerebral injury. Patients who have CKD typically require treatment with EPO to correct the anemia associated with the disease. There is clinical and epidemiologic evidence that environmental or occupational lead exposure adversely affects EPO production and results in delayed erythrocyte regeneration after blood loss or blood donation. The study by Grandjean et al. (1989) described earlier in the discussion of hematopoietic effects ultimately led to that discovery. Although the authors attributed the delay in erythrocyte regeneration to the impairment of heme synthesis by lead, it was later demonstrated in an environmentally exposed population of pregnant women that the effect was due to lead-induced impairment of EPO production (Graziano et al. 1991), in this case in response to the anemia of pregnancy. The relationship between BLL and EPO was later described in lead workers in Austria (Osterode et al. 1999). Thus, occupational lead exposure can have an adverse effect on renal EPO production and the regulation of hematopoiesis.

There is also evidence that lead exposure has adverse effects on the renin-angiotensin-aldosterone system and that these effects may contribute to lead-induced hypertension. A considerable body of literature concerning animal models indicates that lead exposure is associated with an increase in renal renin secretion (Vander 1988). Findings from human studies are more variable, although studies with larger samples have generally found increased plasma renin and increased serum aldosterone, which would be a logical consequence of increased renin secretion. For example, a study of 33 normotensive men, 25 of whom were occupationally exposed to lead for weeks to months (mean BLL 35.6 μg/dL), found positive exponential relationships between BLL and plasma renin activity, angiotensin, angiotensin-converting enzyme, and aldosterone levels (Campbell et al. 1985). A more recent study of 50 occupationally lead-exposed and nonexposed adults in Egypt (BLLs not specified) reported higher serum aldosterone in the exposed than in the nonexposed group and higher plasma renin activity in male workers than in female workers (Shouman and El-Safty 2000).

Summary Findings on Renal Effects

The committee concludes that the evidence is sufficient to infer causal relationships between BLLs under 40 μg/dL (upper acceptable limit in the OSHA standard) and impaired renal function (see Table 4-3) (Staessen et al. 1992; Muntner et al. 2005; Navas-Acient et al. 2009). The adverse effects are manifested by increases in serum creatinine, impaired creatinine clearance, and GFR and by alterations in renal endocrine functioning that may contribute to delayed blood regeneration capacity and hypertension. The committee's conclusions agree with those of NTP (2012) and those proposed by EPA (2012).

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

The adult reproductive system is a critical target for the toxic effects of lead. Men and women at the peak of their reproductive years serve as firing-range personnel. Occupationally relevant reproductive outcomes in lead-exposed men and women may include adverse effects on hormone concentrations, fertility, semen, menstruation, and gonadal histology and architecture. Potential lead-induced developmental effects (such as birth defects, spontaneous abortion, preterm birth, intrauterine growth retardation, low birth weight, and reduced spermatogenesis in exposed offspring) are also relevant.

Potential modes of action of lead reproductive toxicity include disruption of the hypothalamic-pituitary-gonadal axis through reduced luteinizing hormone secretion and reduction in the expression of the steroidogenic acute regulatory protein (Crain et al. 2008; EPA 2012). Lead may also interfere with cation-dependent secondary messenger systems that mediate pituitary hormone release

TABLE 4-3 Key Studies of the Renal Effects of Lead

Health Effects	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
Increase in serum creatinine	459 men selected at random from Normative Aging Study of healthy veterans in greater Boston area	Mean BLL = 8.7 µg/dL	10-fold increase in BLL was associated with increase of 0.08 mg/dL in serum creatinine.	Study of veterans with BLLs in range of interest.	Kim et al. 1996
Impaired creatinine clearance	Random sample of 965 men, 1,016 women in areas with low or high environmental cadmium	Mean BLL = 11.4 µg/dL in men, 7.5 µg/dL in women	10-fold increase in BLL was associated with reduction in creatinine clearance of 10-13 mL/min.	Strong evidence of impaired renal function at relatively low BLLs; well-done study.	Staessen et al. 1992
CKD based on GFR clinical cutpoint	10,000 adults from NHANES study (1999-2002)	Highest quartile of BLL was >2.47 µg/dL;[a] lowest quartile was <1.06 µg/dL	CKD was 2.72 times more likely in highest than in lowest quartile of BLL.	Strong evidence of effects in large US population.	Muntner et al. 2005
CKD, albuminuria	15,000 adults from 1999-2006 NHANES studies	Highest quartile of BLL was >2.4 µg/dL;[a] lowest quartile was <1.1 µg/dL	CKD was 1.56 times more likely in highest than in lowest quartile of BLL.	Strong evidence from NHANES data.	Navas-Acien et al. 2009
Creatinine clearance, GFR	820 women in Lund, Sweden	Mean BLL = 22 µg/dL (range 11-46 µg/dL)	For each 1 µg/dL in BLL, GFR declined by 0.20 mL/min, creatinine clearance by 0.18 mL/min.	Well-done study that adjusted for many covariates.	Åkesson et al. 2005
Decline in GFR over 4 y	121 CKD patients in Taiwan	3.4, 4.9 µg/dL in those with low, high chelatable lead burden, respectively, as assessed with $CaNa_2EDTA$	Each increase of 1 µg/dL in BLL led to reduction in GRF of 4.0 mL/min.	Four-year longitudinal study.	Yu et al. 2004

Various clinical measures of renal function	803 lead workers, 135 controls in South Korea	Mean BLL in workers = 32 µg/dL; tibia lead, DMSA chelatable lead also measured	Variable, depending on exposure metric and model covariates.	Adverse associations between tibia lead and renal-function markers (especially in older workers).	Weaver et al. 2003
Various clinical measures of renal function	537 current or former lead workers derived from above population of 803 in South Korea; evaluated about annually for 3 y	Mean BLL in workers = 31 µg/dL; tibia lead = 35 µg/g bone mineral	Variable, depending on exposure metric and model covariates.	Blood and bone lead were significantly associated with changes in renal function.	Weaver et al. 2009
Delayed blood regeneration due to inadequate renal erythropoietin production	25 lead workers, 25 age-matched controls in Denmark	Mean BLL = 44 µg/dL in workers, 2.7 µg/dL in controls	Two-week delay in restoring hemoglobin concentration after losing 450 mL of blood.	This has implications for those who might experience blood loss for any reason.	Grandjean et al. 1989
Increased plasma renin activity, angiotensin, angiotensin-converting enzyme, aldosterone	33 normotensive men, 25 occupationally exposed to lead	Mean BLL = 35.6 µg/dL (range 8.3-62.1 µg/dL)	5-fold increase in plasma renin activity across BLL range; 6-fold increase in angiotensin.	Changes in renin-angiotensin system may contribute to hypertension in personnel.	Campbell et al. 1985

Abbreviations: BLL, blood lead level; $CaNa_2EDTA$, calcium disodium ethylenediamine tetraacetic acid; CKD, chronic kidney disease; DMSA, 2,3-dimercaptosuccinic acid; GFR, glomerular filtration rate; NHANES, National Health and Nutrition Examination Survey.

[a]It is important to appreciate that BLL in adulthood probably captures cumulative dose to some degree.

and storage. Lead-induced production of reactive oxygen species (ROS), calcium mimicry, and binding to protein sulfhydryl groups are potential biochemical modes of action (EPA 2012). And lead can alter zinc, iron, and potassium function in cells (Sun and Suszkiw 1994; Lal et al. 1996; Lasley and Gilbert 1996).

Pharmacokinetic modes of action warrant consideration. Lead is consistently detected in human testes, epididymides, prostate, and seminal vesicles (Oldereid et al. 1993). Of particular concern is the accumulation of lead in the epididymides because this results in long-term exposure of semen to lead. Lead enters human sperm (and probably related cells at earlier stages of differentiation) through voltage-gated potassium and calcium channels (Benoff et al. 2007). Different isoforms of those channels differ in their ability to transport lead, and expression of channel isoforms likewise differ among men. Exposure to a given BLL may therefore result in different intracellular lead concentrations in male germ cells and have different effects on fertility. Pregnant women can transfer lead to their fetuses, as demonstrated by the strong correlation between maternal and umbilical cord BLLs (Gardella 2001). During pregnancy and after birth, skeletal lead stores are an important contributor to maternal BLLs (Gulson et al. 1999). Lead levels in breast milk increase with increasing maternal BLL, and this poses an additional risk to the neonate (Li et al. 2000).

Conclusions from the 2012 Environmental Protection Agency and 2012 National Toxicology Program Lead Documents

Environmental Protection Agency 2012 Integrated Science Assessment for Lead (Second External Review Draft)

EPA's review of recent epidemiologic studies of environmental lead exposure and reproductive function concludes that there is strong evidence that increasing lead exposure is associated with reduced male fecundity or fertility, decreases in sperm count, and reduced sperm velocity and motility. EPA's draft report further concludes that deleterious associations with sperm count and quality are observed in occupationally exposed men who have mean BLLs as low as 20-45 µg/dL. EPA concluded that there was some association between maternal lead exposure and low birth weight; toxicologic studies in animals have shown that lead exposure during early fetal development can result in abnormal retinal development and alterations in the developing hematopoietic and hepatic systems.

National Toxicology Program 2012 Monograph on Effects of Low-Level Lead

The NTP concluded that there was inadequate evidence to conclude that BLLs under 10 µg/dL are associated with adverse effects on reproduction in men. There was, however, sufficient evidence to conclude that BLLs of 15

µg/dL and over are associated with adverse effects on sperm or semen and that BLLs of 20 µg/dL and over are associated with delayed conception time. Decreases in sperm count, density, and concentration were seen in men who had mean BLLs of 15-68 µg/dL. The NTP also concluded that there was sufficient evidence that maternal BLLs under 5 µg/dL are associated with reduced fetal growth or lower birth weight. There is limited evidence that maternal BLLs under 10 µg/dL are associated with preterm birth and spontaneous abortion. Prospective studies reviewed by the NTP provided limited evidence that prenatal exposure to BLLs under 10 µg/dL is associated with reduced postnatal growth in children. The NTP recognized that its conclusions about prenatal lead exposure were confounded by possible continuing postnatal exposure to lead (associated with BLLs under 10 µg/dL) that is also associated with reduced postnatal growth in children.

Other Studies Considered

Animal Toxicology Studies

The committee considered several key pieces of evidence derived from animal studies in its deliberations. Those studies identified effects on hormone function, gonad structure, and developmental (teratogenic) responses that have been incompletely examined in human epidemiologic investigations and provided additional weight of evidence that supports the committee's conclusions.

In male rodents and monkeys, long-term lead exposure resulting in BLLs over 20 µg/dL reduced serum concentrations of luteinizing hormone, follicle-stimulating hormone, testosterone, estradiol, and other reproductive hormones (Foster et al. 1993; Allouche et al. 2009; EPA 2012). Decreased reproductive-organ weight, histologic changes in the testes and germ cells, reduced fecundity, and decreased numbers of uterine and ovarian estrogen, luteinizing hormone, and follicle-stimulating hormone receptors occur in animals after lead exposure (Wiebe and Barr 1988; Wiebe et al. 1988; Singh et al. 1993; Batra et al. 2001; Wang et al. 2008; Anjum et al. 2011). Dumitrescu et al. (2008) demonstrated that exposure of female rats to lead at 150 ppb before mating and during pregnancy caused a concentration-dependent shift in the male-to-female sex ratio of the offspring, but this effect has not been replicated in other studies (Ronis et al. 1998).

Lead induces reproductive and developmental effects in laboratory rats after gestational or lactational exposure. Many of the effects occur in a concentration-dependent manner and have been observed at maternal BLLs that do not result in overt maternal toxicity (under 40 µg/dL). Animal studies have further demonstrated that effects of lead exposure during early development include impairment of retinal development and alterations in the developing hematopoietic and hepatic systems. Toxicology studies in male animals have reported de-

layed sexual maturity, as seen in reduced prostate weight and other reproductive outcomes, reaching significance at BLLs of 34 µg/dL (Sokol et al. 1985).

Animal models are important for predicting human reproductive and developmental toxicity (Tyl 2005; Cooper and Doerrer 2010; Daston and Knudsen 201), but, because of differences in such things as pharmacokinetics and hormonal regulaton of parturition, their validity in modeling human pathologic conditions (in particular, conditions that are of a complex and multifactorial nature, such as preterm birth) must be considered in interpreting the data. The use of animal studies for lead risk assessment has important limitations. For example, human spermatogenesis is far less efficient than that of other mammals, with efficiency being defined as the estimated number of spermatozoa generated per day per gram of testicular parenchyma (Amann 1970; Johnson 1995; Johnson et al. 2000). Teratozoospermia (abnormal sperm morphology) is more common in humans than in animal models (Hafez 1987; WHO 2010).Although it remains unclear what animal species or strain is best for modeling lead effects on humans, the only consistent findings on the effects of lead exposure in the male animal and the human male are related to decreased sperm motility and increased spontaneous acrosome loss. Thus, one could infer that lead exposure may have a more deleterious effect on sperm function than on sperm production, and thus affect male fertility status, than previously thought.

Male Reproductive Effects

The committee considered two broad types of human epidemiologic studies during its deliberations: occupational studies and studies of male patients in infertility clinics. In general, the committee focused its review on studies in which BLLs were reported. It also considered studies in which lead concentrations in seminal fluid (total ejaculate, including fluids produced by the accessory sex glands—seminal vesicles and prostate—and sperm) or seminal plasma (fluid remaining after sperm are removed from the ejaculate) were measured.

Several studies report an association between occupational lead exposure and decreased sperm count, velocity, and motility; greater haploidy of sperm DNA; and morphologically apparent sperm abnormalities. The studies were of men who worked in battery- or paint-manufacturing plants for 10-15 years. Workers in the highest-exposure groups had mean BLLs of 68.26 µg/dL (Naha and Manna 2007) and 77.22 µg/dL (Naha and Chowdhury 2006). Nonoccupationally exposed controls had mean BLLs of 10-15 µg/dL. A Taiwanese study reported that male lead-battery workers who had BLLs of 45 µg/dL or over had more sperm head abnormalities, greater sperm DNA denaturation, and greater sensitivity to denaturation than workers who had BLLs under 25 µg/dL (Hsu et al. 2009). In contrast, no association was observed between lead exposure and changes in semen volume; sperm count, motility, or velocity; or ROS production in the same study. Kasperczyk et al. (2008) reported that Polish metalworkers who had a mean BLL of 53.1 µg/dL had lower sperm motility and higher semi-

nal lipid peroxidation than nonexposed office workers who had a mean BLL of 8.47 µg/dL. The authors also reported no difference in semen volume, sperm count, or sperm morphology among or between the groups. One problem associated with these occupational studies is that many of the control groups were reported to have BLLs over 8 µg/dL, so it was difficult to assess the effects of very low lead exposures and to determine whether there actually is a "safe" level of lead exposure. That may help to explain why epidemiologic studies have produced conflicting findings.

Several studies have examined men who were exposed to lead nonoccupationally. In general, BLLs of nonexposed, nonsmoking subjects recruited from the general population or from infertility clinics were generally lower than those seen in the occupational studies. BLLs (up to about 15 µg/dL) in Croatian men without occupational exposure to lead or other metals were associated with increased percentages of pathologic sperm, including wide sperm and round sperm (Telisman et al. 2007). Chia et al. (1992) reported that men who were attending an andrology clinic in Singapore and had reduced sperm motility had higher BLLs (mean 7.2 µg/dL) than men who had normal sperm motility (mean 5.1 µg/dL). However, blood cadmium concentration was also increased in this study population (Chia et al. 1992). Other studies of men who were attending infertility clinics reported no association between BLL (mean 8-15 µg/dL) and alterations in sperm characteristics (Xu et al. 1993; Meeker et al. 2008; Mendiola et al. 2011). The largely negative studies may reflect in part the use of sperm counts as the primary indicator of lead-associated infertility effects. There is strong evidence that human sperm count displays geographic, regional, and time-dependent decreases (Carlsen et al. 1992; Swan 2006). Spermatogenesis is testosterone-dependent. Consistent with the reports of declining sperm counts, Travison et al. (2007) reported that serum testosterone is declining over calendar time (for example, in birth cohorts) in American men and that the decline is age-independent. Therefore, serum hormone concentrations are also inappropriate as biomarkers of the potential antireproductive effects of lead in the human male. Another weakness of the studies is the failure to control for untreated fertility issues in the female partners of the study subjects and for the effects of other metal contaminants.

Several relatively recent investigations have focused on semen lead concentration as a biomarker, as has long been the case in the reproduction community (see review by Benoff et al. 2000). Mendiola et al. (2011) reported an association between semen lead concentration and increased percentage of immotile sperm; however, the analysis failed to adjust for exposure to other metals. Slivkova et al. (2009) reported a negative correlation between semen lead concentration and pathologic changes in sperm (specifically, flagellum ball), but no correlations with other sperm alterations were observed. There is additional evidence that increasing seminal plasma lead concentrations are associated with alterations in two sperm functions required for fertilization: decreased motility, which is the major determinant of pregnancy outcome (Shulman et al. 1998; Stone et al. 1999), and increased spontaneous acrosome loss (Benoff et al. 2000,

2003a,b). The latter process can be mimicked by incubating fertile donor sperm in medium containing lead at levels seen in seminal plasma (Benoff et al. 2000, 2003a,b). One study has shown that BLLs do not correlate with the concentration of lead in male reproductive tissues or any somatic tissues examined (Oldereid et al. 1993), but it remains unclear whether BLL or seminal plasma lead concentrations are equally predictive of lead-induced reproductive toxicity in men. Therefore, the committee focused its attention on the use of BLL, commonly assumed to have general applicability as a biomarker of lead exposure.

Female Reproductive Effects

Lead exposure was found to affect female reproductive function in both epidemiologic and toxicologic studies. BLL was associated with changes in hormone concentrations in women; however, study results varied in the magnitude and direction of the changes. The EPA report (2012) states that the selected studies are inconsistent with respect to associations between lead and fertility but suggest that there is evidence of a direct relationship between female lead concentrations and decreased fertility rates. Although the toxicologic and epidemiologic studies examined responsiveness to lead exposure during different exposure periods, both lines of evidence support the conclusion that exposure to lead affects some aspects of reproductive function in women.

The previous EPA (2006) report stated that lead exposure does not result in female sterility but can disrupt female fertility. That finding is supported by animal studies and epidemiologic investigations. Studies by Bloom et al. (2010, 2011) provided evidence that higher BLL was not associated with oocyte fertilization but that embryo cell number was lower in association with higher BLL. Chang et al. (2006) found that women who were seeking care at a fertility clinic had higher BLLs than women who delivered normally at a nearby medical center. In that study, the adjusted effect estimates threshold BLL was 2.5 µg/dL. Al-Saleh et al. (2008a) reported that lower rates of fertilization were associated with BLL but not with follicular lead concentrations. In contrast, Silberstein et al. (2006) found that lead concentrations in the follicular fluid exceeded those in blood and that even at low concentrations the presence of lead in follicular fluid was inversely associated with pregnancy. Those studies are limited in that they each used women who were seeking fertility assistance in an in vitro fertilization clinic where only a woman's lead levels were considered and thus ignored the potential contribution of lead to sperm dysfunction. The study by Silberstein et al. suffers from a small sample, the fact that follicular and plasma lead concentrations did not correlate well with each other, and potentially confounding factors (such as smoking and occupation) that were not considered in the analysis.

Yin et al. (2008) examined whether there is an association between plasma lead concentrations and anembryonic pregnancies (spontaneous abortion in the first trimester associated with a normal amniotic sac but loss of the embryo). Women who delivered at term had mean plasma lead lower than that of women

who had anembryonic pregnancies. Lamadrid-Figueroa et al. (2007) found that women in the highest one-third for plasma:blood lead ratio had a greater risk of spontaneous abortion than women in the lowest one-third, but no associations were found if whole blood or plasma alone was used. Gundacker et al. (2010) reported that women who had miscarried during a previous pregnancy had higher placental lead concentrations (39 µg/kg) than women who had not miscarried in the past (27 µg/kg).

Most of the epidemiologic studies in the EPA report were cross-sectional, so it is difficult to ascertain the most sensitive period in a woman's lifetime, when lead exposure would be most detrimental to reproductive health.

The NTP (2012) report points out that although current studies provide some level of evidence of an association between lead and adverse effects on female reproductive health, it cannot now be determined whether there is a critical window for exposure. Furthermore, it is difficult even to attempt to determine when a sensitive period might be inasmuch as older adults were likely to have had BLLs over 10 µg/dL as children. The NTP report cites a large cohort study of mother-infant pairs that did not find an association between BLLs (mean 2.1 µg/dL) and preterm birth (Zhu et al. 2010). The NTP's conclusion of a limited association between low-level lead exposure and spontaneous abortion was based predominantly on a single case-control study of women who had occupational exposure to lead (Borja-Aburto et al. 1999). Another possible weakness in both studies was the small number of available datasets with which to study responses in humans. In addition, the use of in vitro fertilization clinic data takes a woman's BLL into account only when there are problems with fertility without considering possible problems with male fertility that may be associated with BLL. Moreover, in vitro fertility clinic data represent only women who are actively seeking help for fertility and may not be representative of all women of child-bearing age.

The NTP concluded that there was limited evidence that BLL under 5 µg/dL is associated with delayed puberty. That conclusion was based in part on a South African longitudinal birth-to-20 cohort study that found that a BLL of 5 µg/dL or over was significantly associated with delayed breast and pubic-hair development (according to Tanner staging) and with age at menarche (Naicker et al. 2010). The association was significant even after adjustment for socioeconomic factors and anthropometric measurements. Evidence of an association between low lead exposure and hormone markers of delayed onset of puberty in girls is emerging (Gollenberg et al. 2010).

The NTP (2012) concluded that there was sufficient evidence of an association between maternal BLL under 5 µg/dL and reduced fetal growth and low birth weight (under 2,500 g after at least 37 weeks of gestation). That association is supported by several prospective studies that measured maternal BLL during pregnancy (Gundacker et al. 2010), a large retrospective cohort study (over 43,000 mother-infant pairs) that reported a mean maternal BLL of 2.1 µg/dL (Zhu et al. 2010), and a number of cross-sectional studies of maternal or umbilical cord blood lead at delivery (Bellinger et al. 1991).

Although the results are not entirely consistent among studies, the evidence on maternal or umbilical cord blood lead (under 10 µg/dL) and the large number of studies led the NTP to conclude that there was sufficient evidence of an association between maternal BLL under 10 µg/dL and reduced fetal growth and low birth weight. In contrast, the NTP concluded that there was only limited evidence that maternal BLL under 10 µg/dL is associated with spontaneous abortion and preterm birth. Although a number of prospective and cross-sectional studies have reported an association between prenatal BLL under 10 µg/dL and preterm birth, the conclusion of limited evidence was based primarily on inconsistency of the data and a large study of mother-infant pairs that failed to find the same relationship. EPA (2012) also concluded that there was little evidence to support an association between maternal or paternal lead exposure and the incidence of spontaneous abortion.

Prenatal and Postnatal Developmental Effects

Studies of the adverse developmental effects of lead exposure in utero and during the immediate postpartum neonatal period were considered relevant to the committee's charge. The literature base is extensive, and a complete review was deemed outside the committee's charge. Rather, it selected studies that examined different developmental end points. Many of the longitudinal studies measured umbilical BLL at birth and grouped infants as having had "low" exposure (for example, under 3 µg/dL), "medium" exposure (for example, 6-7 µg/dL), or "high" exposure (10 µg/dL or above). Postnatal development was then assessed at various intervals.

Detrimental effects of lead exposure on IQ and cognitive development have been observed in many studies (Baghurst et al. 1992; Bellinger 2000; Wasserman et al. 2000; Al-Saleh et al. 2009; Jedrychowski et al. 2009) and suggest the presence of a causal association between lead exposure and adverse developmental neurologic effects. Individual studies diverge in their ability to identify windows of susceptibility. In some, a lack of association between postnatal BLL and concurrent cognitive or other development scores was observed (e.g., Al-Saleh et al. 2009), but the finding suggests that in utero lead exposure may account for the effects seen. Other studies (e.g., Wasserman et al. 2000) have suggested that prenatal and postnatal exposures that occur at any time during the first 7 years of life are likely to be independently associated with small decrements in later IQ scores.

Studies have shown an association between umbilical blood lead concentration under 10 µg/dL and reduced head circumference (Al-Saleh et al. 2008b), effects on infant attention (Plusquellec et al. 2007), abnormal reflexes and abnormal results on neurologic soft signs scales (Ernhart et al. 1986), reduced body-weight gain (Sanin et al. 2001), and decreased body-mass index (NTP 2012). Deficits in visual function in children were also seen at umbilical blood lead levels as low as 10.5 µg/dL (Rothenberg et al. 2002). Increased maternal

tibia lead concentration 1 month after birth has been associated with decreased infant body weight at birth (González-Cossío et al. 1997). Results in a Mexico City cohort showed associations between maternal BLL at midpregnancy (mean 7.7 μg/dL) and brainstem auditory evoked responses in newborns, 3-month-old infants, and 67-month-old children (Rothenberg et al. 2000). Studies of human male sexual development are few, but the available data (for example, on timing of puberty onset based on testicular volume, delays in axillary and pubic-hair development, penile staging, and mean testosterone level) provide suggestive evidence that even low lead exposure (based on BLLs of over 5 μg/dL to under 10 μg/dL) is associated with delayed puberty in offspring (Hauser et al. 2008).

Summary Findings on Reproductive and Developmental Effects

The committee concludes that the evidence is sufficient to infer causal relationships between BLLs over 40 μg/dL and adverse effects on sperm and semen, including decreased sperm count, reduced sperm motility, and increased morphologic abnormalities (see Table 4-4). The committee concludes that the evidence to infer causal relationships between BLLs under 40 μg/dL and adverse effects on sperm and semen is limited. The committee also found strong evidence of a causal relationship between prenatal maternal BLLs under 10 μg/dL and adverse developmental effects in infants and children and sufficient evidence of an association between maternal BLLs under 5 μg/dL and reduced fetal growth and low birth weight (see Table 4-5). The committee's conclusions are consistent with those of EPA and the NTP.

IMMUNOLOGIC EFFECTS

Animal studies that illustrate the capacity of lead at levels below those recognized as overtly toxic to modify immune function and compromise host resistance against infectious disease date back at least 50 years (Mishra 2009). Age-based exposure studies also suggest that BLLs previously thought safe (under 10 μg/dL) may be associated with later-life immune alterations (Dietert and Piepenbrink 2006). The potential for adverse human health effects of lead-induced alterations in the immune system is rapidly emerging as a matter of increasing scientific and public concern. Although studies of the effects of lead exposure on children are plentiful, few have examined effects on the adult immune system, and their results have often been contradictory. There are, however, compelling indications from epidemiologic and worker studies that lead can induce immune alterations in exposed humans (Fischbein et al. 1993; Undeger et al. 1996; Kuo et al. 2001; Qiao et al. 2001; Mishra et al. 2003; Mishra 2009; Garcia-Leston et al. 2011), particularly changes in B lymphocytes; in the nature, extent, and spectrum of circulating antibodies; and in T-lymphocyte profiles.

TABLE 4-4 Key Studies of the Male Reproductive Effects of Lead

Health Effects	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
Sperm abnormalities	Men (n = 80; mean age = 29.2 y) working at a Taiwanese battery plant for mean work duration of 1.7 y	Mean BLLs in groups were 21.3 (10.5-24.9), 37.3 (26.9-45.0), 53.3 (45.7-70.9) µg/dL; overall mean BLL = 40.2 µg/dL	ANOVA (p values <0.05) for: increased sperm head or neck abnormalities in highest-exposure group, lead-induced increases in sperm chromatin structure assay (αT, COMPαT) in both exposure groups.	Data suggesting negative outcome in group of relevant age.	Hsu et al. (2009)
Reduced sperm motility	Healthy, nonsmoking, fertile men (n = 63, mean age in three groups were 34.4 to 38.3 y) that worked at a Polish zinc and lead metalworks for an average of about 13-14 y	High-exposure workers: mean BLL = 53.1 (40-81) µg/dL, PbS = 2.02 µg/dL; low-exposure workers: mean BLL = 34.7 (25-40) µg/dL, PbS = 2.06 µg/dL; office-worker controls: mean BLL = 8.47 µg/dL, PbS = 1.73 µg/dL	34% reduction in percentage of motile sperm after 1 h in high-exposure group vs controls (p = 0.034).	Clinically important outcome in group of relevant age.	Kasperczyk et al. (2008)
Abnormal sperm	240 Croatian men 19-52 years of age with no occupational exposure to lead or other metals	Median BLL = 4.92 (1.13-14.9) µg/dL	Increase in immature sperm concentration; in percentages of pathologic, wide, round, short sperm; in serum testosterone, estradiol. Decrease in seminal plasma zinc, in serum prolactin.	Data suggesting negative outcome in group of relevant age.	Telisman et al. (2007)

Abbreviations: αT,extent of DNA denaturation per cell; BLL, blood lead level; COMP αT, percentage of sperm with increased sensitivity to DNA denaturation; PbS, seminal plasma lead concentration.

TABLE 4-5 Key Studies of the Female Reproductive Effects of Lead

Health Effects	Population Characteristics	Measures	Adjusted Effect Estimates	Why Study Is Relevant to DOD	Reference
Infertility	Women receiving care in fertility clinic in 2000-2001 or delivering normal infant in nearby medical center in 1999	BLL >2.5 µg/dL	OR (95% CI): ≤2.5 µg/dL, 1.00 (reference); >2.5 µg/dL, 2.94 (1.18, 7.34).	Relevant BLL.	Chang et al. 2006
Achieving fertilization or pregnancy	Women (19-50 y old) undergoing IVF	BLL = 3.34 ± 2.24 µg/dL	OR (95% CI) (unit not given, assume results are per 1 µg/dL): pregnancy, 0.55 (0.23, 1.31); fertilization, 0.30 (0.08, 1.03); in reduced adjusted model for fertilization, OR for BLL was 0.38 (0.14, 0.99).	Relevant BLL.	Al-Saleh et al. 2008a
Oocyte maturity, oocyte fertilization	Women in Study of Metals and Assisted Reproductive Technologies; women referred to Center for Reproductive Health at UCSF for infertility treatment and first IVF procedure	BLL = 0.34-1.5 µg/dL	RR (95% CI) per 1 µg/dL (controlled for cadmium): oocyte maturity (determined by metaphase II arrest), 0.54 (0.31, 0.93); oocyte fertilization, 0.97 (0.66, 1.43).	Relevant BLL.	Bloom et al. 2010
Embryo cell number, embryo fragmentation score	Women in Study of Metals and Assisted Reproductive Technologies; women referred to Center for Reproductive Health of UCSF for infertility treatment and first IVF procedure and who generated embryos	BLL = 0.86 µg/dL	OR (95% CI) per 1 µg/dL (adjusted for mercury and cadmium): embryo cell number, 0.25 (0.07, 0.86); embryo fragmentation score, 1.71 (0.45, 6.56)	Relevant BLL.	Bloom et al. 2011

(Continued)

TABLE 4-5 Continued

Health Effects	Population Characteristics	Measures	Adjusted Effect Estimates	Why Study Is Relevant to DOD	Reference
Anembryonic pregnancy	Women (25-35 y old) at 8-12 weeks of gestation; cases were anembryonic pregnancies, controls were normal pregnancies that resulted in live birth at 37-42 weeks	Maternal BLL after miscarriage in cases, at study enrollment in controls: ≥53 µg/dL	Comparisons between log-transformed BLL of cases, controls with Student's t test had p value of 0.03.	Effects seen when maternal BLL was ≥40 µg/dL.	Yin et al. 2008
Miscarriage	Women who had previous pregnancy and were currently pregnant at gestational age of ≤14 weeks	Maternal BLL = 62.4 µg/dL; plasma lead level = 0.14 µg/dL; plasma:whole blood ratio = 0.22%	IRR for plasma fraction tertiles: 1st tertile, 1.00 (Ref); 2nd tertile, 1.16 (p = 0.61); 3rd tertile, 1.90 (p = 0.015). IRR per 1 SD increase: plasma lead, 1.12 (p = 0.22); BLL, 0.93 (p = 0.56); plasma/BLL ratio, 1.18 (p = 0.02).	Relevant to pregnant instructors on firing ranges; partitioning of lead to plasma heightens risk of placental transfer to fetus, increasing chance for miscarriage.	Lamadrid-Figueroa et al. 2007
Miscarriage	Women recruited during second trimester of pregnancy	Lead in whole placentas	Median placenta lead: 27 µg/kg in women who had not previously miscarried, 39 µg/kg in women who had previously miscarried; p for difference 0.039.	Relevant to pregnant instructors on firing ranges.	Gundacker et al. 2010
Delayed puberty	South African longitudinal (birth to 20 cohort) study (3,273 mothers)	BLL >5 µg/dL; cord blood obtained during 4th stage of delivery; venous blood collected from children 13 y old	Higher BLLs were associated with delayed onset of puberty (p < 0.001).	Relevant BLL; relevant to pregnant instructors.	Naicker et al. 2010

Fetal growth and birth weight	Retrospective cohort study of NY state heavy-metals registry records of women 15-49 y old (43,288 mother-infant pairs)	BLL <10 µg/dL (average BLL = 2.1 µg/dL; median BLL = 2.0 µg/dL)	BLLs of 5, 10 µg/dL associated with average decrease in birth weight of 61 g and 87 g, respectively; model assumed linear relationship between untransformed BLL and gestational age in days; data adjusted for timing of lead test, maternal age, race, smoking, alcohol consumption, economics, parity, infant sex.	Key evidence of effects of BLL <10 µg/dL on birth weight.	Zhu et al. 2010

Abbreviations: BLL, blood lead level; CI, confidence interval; IRR, incidence rate ratio; IVF, in vitro fertilization; OR, odds ratio; RR, relative risk; SD, standard deviation; UCSF, University of California, San Francisco.

The exact mechanisms whereby lead interacts with the immune system remains unclear. However, several effects of lead on the immune system can be explained in the context of activation of the nuclear factor-κB (NF-κB) signal transduction pathway that represents a group of structurally related proteins. NF-κB plays a critical role in triggering and coordinating both innate and adaptive immune responses (Dietert and Piepenbrink 2006). In addition, Fischbein et al. (1993) suggested that lead may exert suppressive effects on lymphocyte functions because of its high affinity for the sulfhydryl groups on T-lymphocyte surface receptors and thus its interference with antigen processing from monocytes to T lymphocytes and consequently with cell-to-cell cooperation. Lead also appears in animal models to affect the immune system indirectly by altering regulation of the endocrine and nervous systems (Mishra 2009).

To provide a better understanding of the studies discussed in this section and to provide perspective on the relevance of such effects on human health, an overview of the immune system is provided below.

Immune System Overview and Early Biologic Effects

The immune system consists of a complex network of cells and soluble mediators that interact in a highly regulated manner to generate an immune response of appropriate magnitude and duration. In animals and humans, immunotoxicity can be manifested in several distinct immunopathologic conditions, including allergic disease, immunodeficiency (immunosuppression), and autoimmunity. On contact with the immune system, chemicals can exert direct toxicity to specific components of the immune system, which can lead either to malfunctioning of the system as a whole or to disruption of regulatory systems that in turn can give rise to immunosuppression or exaggerated responses (manifested possibly as atopy or autoimmunity). In the former case, the immune system responds to the agent as an allergen (of low or high molecular weight), and this results in such disorders as allergic contact dermatitis (Descotes et al. 1995; Luster et al. 2001). In immunodeficiency, the immune system acts as a passive target for the chemical, and the result may be increased incidence or severity of infectious disease or cancer. Autoimmunity, a breakdown in immune tolerance, occurs when the agent directly or indirectly induces an immune response to "self" constituents, such as specific proteins or DNA, that leads to pathologic conditions.

The immune system has three basic components: humoral, cell-mediated, and innate (nonspecific) immune responses. Humoral immunity is primarily associated with B lymphocytes and the production of antibodies, also known as immunoglobulins (Ig). Differentiated B cells produce five Ig isotypes, each with unique structure and function: IgG, IgM, IgD, IgE, and IgA. For example, IgE is associated with allergic type 1 immediate hypersensitivity reactions, and IgA (a secretory antibody) is found in bodily secretions.

In contrast, cell-mediated immunity is associated with T lymphocytes (such as $CD3^+$, $CD4^+$, and $CD8^+$) that develop from pluripotent stem cells in bone marrow and migrate to the thymus to mature and differentiate. As these precursor cells proliferate and differentiate into mature T lymphocytes, they increase their expression of surface CD (cluster of differentiation) markers that confer cell-type specificity. Immature T cells termed double CD negative cells ($CD4^-CD8^-$) lack expression of CD4 and CD8. On activation, one class of mature T cells differentiates into cytotoxic T lymphocytes (CTLs), distinguished by a cell-surface $CD8^+$ marker, that can release cytokines (small molecules that act on cells and stimulate or inhibit their function) and kill tumor- and virus-bearing cells. T cells bearing $CD4^+$ markers recognize antigen on their surface and release signature cytokines. $CD4^+$ cells, critical for immune protection, can be subdivided into T-helper (T_H) cells (T_H1, T_H2, T_H3, and T_H17) that help other immune cells by activating or directing their activities. For example, T_H cells are essential in B-cell antibody class switching, activation and growth of CTLs, and maximizing bactericidal activity of phagocytes (such as macrophages). $CD4^+$ cell populations, classified as either naïve (not exposed to antigen) T lymphocytes ($CD45RA^+$) or activated memory T cells ($CD45RO^+$), also include regulatory cell types, such as natural killer (NK) T cells and T-regulatory cells. T_H cells are subdivided (on the basis of the types of cytokines that they release) into T_H1 and T_H2 phenotypes. Under normal circumstances, the T_H1:T_H2 ratio is balanced. Skewing toward T_H1 or T_H2 responses can result in a hyperinflammatory state or autoimmunity, respectively.

The innate (also known as nonspecific) immune system comprises the cells and mechanisms that defend a host from infection in a nonspecific manner. The cells recognize and respond to pathogens and tumor cells, but, unlike the adaptive immune system, they do not confer long-lasting or protective immunity. A number of critical cell types and soluble mediators are essential for nonspecific immunity. Macrophages and neutrophils play an essential role in the uptake (phagocytosis) and killing of ingested bacterial pathogens, whereas NK cells, also essential for innate immunity, kill virus-infected cells and neoplasms without prior sensitization. Each of those cell types is also an important source of immunoregulatory cytokines that mediate a variety of immune responses and inflammation.

Many immune end points, such as serum cytokine and Ig concentrations, are often used as indicators to predict early biologic effects of chemical-induced immunotoxicity. However, such immune measurements can lack sensitivity, are poorly standardized, or are poorly linked quantitatively to a disease process, so their relevance in assessing immunotoxic effects in humans is poorly established. In addition, translation of such early effects to a pathologic response or a disease phenotype on the basis of the toxicologic paradigm exposure → internal dose → biologically effective dose → early biologic effects → altered structure

and function → clinical disease is often not possible, because of the lack of specificity and persistence of the response.

Conclusions from the 2012 Environmental Protection Agency and 2012 National Toxicology Program Lead Documents

Environmental Protection Agency 2012 Integrated Science Assessment for Lead (Second External Review Draft)

Because of few data on the immunologic effects of lead in exposed adults, EPA's draft assessment relied heavily on animal data and epidemiologic studies in children to support its overall conclusion of a causal relationship between lead exposures and immune system effects in adults. EPA's draft assessment concluded that lead exposure is associated with a broad spectrum of changes in both cell-mediated and humoral immunity that cumulatively promote a T_H2 phenotype and a hyperinflammatory state. The principal conclusions were that lead, at BLLs of 30 μg/dL or under, induced an increased production of T_H2 cytokines, suppressed production of T_H1 cytokines, increased neutrophil infiltration (a marker of inflammation), and increased circulating IgE. In the studies of adults (mostly males) who had occupational lead exposures, the most consistent finding was decreased neutrophil function in workers who had BLLs of 21-71 μg/dL (Valentino et al. 1991). Studies reviewed by EPA also reported a shift toward T_H2 cytokines in workers who had a BLL of 5 μg/dL. Uncertainty exists regarding the contributions of current lead exposures and cumulative lead stores in bone, but recent evidence on adults who had no occupational exposure has demonstrated altered concentrations of allergic IgE and specific cytokines in populations of adults who had BLLs of 1.9-7.0 μg/dL. On the basis of the consistency and coherence of findings across the continuum of related immune measures that demonstrated a stimulation of T_H2 responses, combined with the supporting epidemiologic evidence on children, EPA concluded that there is a causal relationship between lead exposure and immune system effects. No BLLs were noted as part of that conclusion although decreased neutrophil function, increased concentrations of autoantibodies, increased inflammation, and a shift to T_H2 cytokines were observed at BLLs of 30 μg/dL or lower and for some end points as low as 5 μg/dL. Some conclusions drawn by EPA differ from those of the NTP. That probably reflects the fact that data from studies of children and rodent models were used to provide the weight of evidence for EPA's conclusions.

National Toxicology Program 2012 Monograph on Health Effects of Low-Level Lead

The NTP concluded that there was inadequate evidence on adults to support a causal relationship between a BLL under 10 μg/dL and any immune end points, including IgE, allergy, and other hypersensitivity reactions. That conclusion was

reached because of the lack of studies of the relationship between immune function and lead in human adults and because most of the studies reported changes only in observational characteristics, such as immune-cell profiles or Ig concentrations, rather than effects on immune function (such as lymphocyte proliferation, phagocytosis of infectious agents, and NK tumoricidal activity), which is linked more closely with pathologic response or human disease. Even in those cases, however, there was inadequate evidence of an association owing to a general lack of investigations at lower BLLs and inconsistency in available data. The metric of bone lead could have been relevant in terms of a cumulative dose, but very few studies that examined changes in immune end points used non-BLL metrics.

Other Studies Considered

Alterations in the immune response that can be easily studied in humans are limited and are primarily reflective of changes in circulating leukocyte profiles and Ig concentrations. Some studies of lead-exposed workers have reported lead-associated differences in serum Ig concentrations, percentages of $CD4^+$ T_H cells, increased circulating B-lymphocytes, decreased NK cells, and impaired lymphoblastogenesis (Ewers et al. 1982; Horiguchi et al. 1992; Fischbein et al. 1993; Queiroz et al. 1993; Undeger et al. 1996; Pinkerton et al. 1998; Basaran and Undeger 2000; El-Safty and Metwally 2000; Kuo et al. 2001; Qiao et al. 2001; Ayatollahi 2002; Mishra et al. 2003, 2006; Heo et al. 2004; Valentino et al. 2007; Mishra et al. 2010; Garcia-Leston et al. 2011). In contrast, other human investigations at similar BLLs demonstrated opposite or no effects on the same characteristics (Horiguchi et al. 1992; Queiroz et al. 1994; Pinkerton et al. 1998; Heo et al. 2004; Mishra et al. 2006; Freije and Dairi 2009). Some results of relevant studies that demonstrated early immunotoxic effects in lead-exposed workers who had BLLs of 40 µg/dL or under are described in brief below.

El-Safty and Metwally (2000) found reduced serum IgA, IgM, and IgG concentrations in lead-exposed plumbers who had an average BLL of 39 µg/dL. Studies by Mishra et al. (2006) supported the finding on circulating Ig and further demonstrated that lead-exposed workers who had an average BLL over 10 µg/dL had increased serum IgA. Fischbein et al. (1993) reported alterations in circulating blood mononuclear-cell profiles and lymphocyte function in firearms instructors. Results of that highly relevant study demonstrated that people who had an average BLL of 25 µg/dL or under, and to a greater extent those who had a BLL over 25 µg/dL, had lower concentrations and lower functional integrity of $CD4^+$ T_H lymphocytes than healthy nonexposed controls. Specifically, the absolute percentage and number of $CD3^+$ and $CD4^+$ cells were statistically significantly reduced, whereas those of $CD8^+$ cells were unchanged. Functional integrity of T cells, as determined by proliferative responses to mitogens, was impaired, whereas that of T-cell-dependent B-lymphocyte function appeared to be within the normal range at all stages of maturation. Another study (Sata et al. 1997) demonstrated that circulating immune cell profiles were increased in lead-exposed male workers, concentrations of B lymphocytes were positively associ-

ated with BLL (average 39 μg/dL), serum IgG was negatively associated with cumulative lead exposure, and naïve memory T cells ($CD3^+/CD45RA^+$) were positively associated with cumulative lead exposure. In a study of Portuguese workers that evaluated immune cell profiles, Garcia-Leston et al. (2011) demonstrated a significant decrease in percentages of $CD8^+$ cells with a concurrent increase in the $CD4^+$:$CD8^+$ ratio in exposed people who had BLLs of 40 μg/dL or higher. In a clinical context, this finding could be significant (although the extent of $CD8^+$ suppression needed for a clinical outcome is unknown) inasmuch as a decrease in $CD8^+$ cells could increase susceptibility to viral infections or decrease antitumor immune mechanisms.

Studies of Turkish storage-battery workers who had a median BLL of 75 μg/dL indicated that it was associated with statistically significant decreases in T_H cells, serum IgG, IgM, and some serum complement components (Basaran and Undeger 2000). In vitro functional aberrations, including changes in neutrophil chemotaxis and random movement, were also noted in the workers. The latter findings were in keeping with the study by Queiroz et al. (1993) that demonstrated defective neutrophil function (chemotaxis and production of ROS) in workers who had a lower average BLL of 41 μg/dL (range 14.8-91.4 μg/dL). Impaired neutrophil movement was thought to be due to lead-induced changes in cell membrane fluidity.

Although most worker studies have examined the immunotoxic effects of lead exposure on men, a study by Qiao et al. (2001) examined women who worked an average of 12 years in printing houses in China. The mean air lead concentration was about 25 (± 19) $\mu g/m^3$, and average BLLs of the workers were about 29 (± 15) μg/dL; the study referent group had an average BLL of 12.4 μg/dL. Assessments of circulating lymphocyte subset concentrations in both referent and lead-exposed women indicated that "memory" T_H cell levels were increased in the exposed workers, whereas NK-cell and B-cell concentrations were statistically significantly reduced. The reduction in blood NK cells in lead-exposed women agrees with the results of Sata et al. (1997), who examined circulating NK cells in male workers who had an average BLL of 18 μg/dL (range 7-35 μg/dL). Also in that study, BLL correlated significantly with serum IgA and IgE concentrations; IgE levels were greatest in workers who had BLLs over 60 μg/dL. In a study that examined battery workers in Korea (Heo et al. 2004), serum IgE concentration correlated significantly with BLL; values were statistically significantly higher in workers who had BLLs of 30 μg/dL or higher than in those who had BLLs under 30 μg/dL. In a study of lead-exposed workers who had BLLs of 9-46 μg/dL, Valentino et al. (2007) examined changes in cytokine concentrations. The results demonstrated that workers had statistically significantly higher concentrations of the anti-inflammatory cytokine interleukin-10 (IL-10) and a tendency toward higher concentrations of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) in occupationally exposed male workers than in sex-matched and age-matched controls.

Summary Findings on Immunologic Effects

The committee concludes that the evidence is inadequate to infer a causal relationship between BLLs under 40 µg/dL and immunotoxicity related to clinical disease (see Table 4-6); this conclusion agrees with the NTP's findings (2012). Although there is compelling evidence of early biologic effects and some effects linked with alterations in immune structure or function, there is insufficient evidence to link these early immune effects with clinical disease. Studies that can relate increased serum IgE concentrations to clinical indicators of allergy in lead-exposed adults would be needed to link immune measures with a specific pathology better. Because early biomarkers of immunotoxicity are observed in lead-exposed humans who have BLLs under 40 µg/dL, effects of lead on the human immune system should be re-evaluated as new research emerges.

CARDIOVASCULAR EFFECTS

The cardiovascular system is a primary target of lead toxicity. Experimental studies and epidemiologic studies have consistently suggested that lead exposure can increase the risk of cardiovascular disease, in particular increased blood-pressure readings and hypertension, even at low levels (BLLs under 10 µg/dL). Potential modes of action include oxidative stress through increased ROS production and inactivation of nitric oxide; hormonal and blood-pressure regulatory system dysfunction through alteration of the adrenergic and renin-angiotensin systems; vasomodulation through increases in vasoconstrictor prostaglandins and decreases in vasodilator prostaglandins; and cellular signaling disruption (Vaziri 2008; EPA 2012). Plasma total homocysteine, a documented risk factor for cardiovascular disease, has also been associated with lead exposure (Schafer et al. 2005; Chia et al. 2007; Yakub and Igbal 2010). Key cardiovascular outcomes and effects considered by the committee included changes in blood pressure, hypertension, pulse pressure, heart-rate variability, electrocardiogram (ECG) conduction abnormalities, peripheral arterial disease, coronary heart disease, myocardial infarction, stroke, and cardiovascular mortality.

Conclusions from the 2012 Environmental Protection Agency and 2012 National Toxicology Program Lead Documents

Environmental Protection Agency 2012 Integrated Science Assessment for Lead (Second External Review Draft)

EPA concluded that there is sufficient evidence of an association between lead exposure and adverse cardiovascular outcomes, especially increased blood pressure and hypertension. EPA's draft report also suggested that bone lead concentration, an indicator of cumulative exposure, is associated with hypertension

TABLE 4-6 Key Studies of the Immunologic Effects of Lead

Health Effects	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
Significantly increased memory T cells; decreased percentage of NKC, B lymphocytes	Women working in printing houses in Shanxi Province, China (mean age 34 y)	Mean BLL = 28.6 µg/dL (mean air lead = 25 µg/m^3)	$p < 0.01$ for NKC, B lymphocytes compared with controls.	Relevant to BLL of instructors on firing ranges.	Qiao et al. 2001
Significantly increased plasma IL-10 TNF-α	Male workers with occupational exposure to lead (30-61 y old)	Low-exposure group: BLL = 3.9 (± 1.8) µg/dL, ALAD = 265.2 U/mL, ZPP = 5.5 µg/dL; high-exposure group: BLL = 9.7 (± 4.2) µg/dL, ALAD = 224.6 U/mL, ZPP = 26.2 µg/dL	$p < 0.05$ for IL-10, TNF-α for both low and high BLL groups compared with nonexposed workers.	Relevant to BLL of instructors on firing ranges.	Valentino et al. 2007
Significantly increased serum IgA	Lead-exposed males in battery-recycling industries (median age 27 y)	BLL >10 µg/dL	$p < 0.05$ for serum IgA concentrations compared with controls.	Relevant to BLL of instructors on firing ranges.	Mishra et al. 2006
Significantly increased percentage of $CD4^+$ cells, decreased immune naive memory T cells ($CD45^+RA^+$)	Male workers driving 3-wheeler vehicles or working in battery-reconditioning plant	BLL = 6.7 µg/dL in drivers; BLL = 132 µg/dL in battery workers; BLL = 4.5 µg/dL in controls	$p < 0.001$ for percentage of $CD4^+$, $CD4^+$:$CD8^+$ ratio; $p < 0.05$ for naive memory T-cell differences.	BLL in drivers relevant to that of instructors on firing ranges.	Mishra et al. 2010
Significantly reduced salivary IgA; negative correlation between BLL and serum complement, IgG	Male workers in battery plant, lead smelter in West Germany	Mean BLL = 51.4 µg/dL in exposed workers; BLL range = 6.6-20.8 µg/dL in reference subjects	$p = 0.008$ for salivary IgA compared with referent group.	Relatively similar BLL to those of firing-range instructors.	Ewers et al. 1982

Significantly increased serum IgE	Male battery-manufacturing workers in Korea	Mean BLL ≥30 µg/dL	$p < 0.05$ for IgE levels compared with controls.	IgE is classic hallmark of type I hyersensitivity, and increase is associated with allergies.	Heo et al. 2004
Significantly increased memory T cells, increased CTL cells	Male lead workers (33-67 y old)	Mean BLL = 19 µg/dL (range = 7-50 µg/dL)	$p < 0.05$ for changes in memory T, CTL cells (age, smoking covariates).	Relevant to BLL of firing-range instructors.	Sata et al. 1998
Significantly reduced percentage of $CD3^+$, $CD4^+$ cells; reduced proliferation of T lymphocytes; decreased HLA responsiveness	Firearms instructors	High-exposure group (≥25 µg/dL), mean BLL = 31.4 (± 4.3) µg/dL; low-exposure group (<25 µg/dL), mean BLL = 14.6 (± 4.6) µg/dL	$p < 0.002$ for changes in $CD3^+$ cells, $CD4^+$ cells, CD4:CD8 ratio in low-exposure group; $p < 0.01$ for changes in HLA in low-exposure group; extent of change was greater in high-exposure group.	Same occupation as DOD population.	Fischbein et al. 1993
Significant decrease in percentage of $CD8^+$ cells; increased $CD4^+$:$CD8^+$ ratio	Portuguese workers employed in inorganic lead plants for different durations	Average BLL = 32 µg/dL; average ALAD activity = 42 U; average ZPP = 52 µg/dL	$p < 0.05$ for changes in $CD8^+$ lymphocytes, CD4+:CD8+ ratio.	Most recent study with BLLs similar to those measured in firing-range instructors.	Garcia-Leston et al. 2011
Significantly reduced neutrophil function (chemotaxis, random movement); reduced neutrophil-associated oxidative stress	Male workers employed in storage-battery plants for average of 4 y	Average BLL = 41.1 ± 12.6 µg/dL in 22 workers; urinary ALAD <6 mg/L	$p < 0.001$ for chemotaxis.	Relevant to BLL of firing-range instructors; changes in neutrophil function noted as key indicator of lead-induced changes in animal models.	Queiroz et al. 1993

(Continued)

TABLE 4-6 Continued

Health Effects	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
Significantly higher percentage of circulating monocytes, reduced $CD8^+$ cells; percentage of B cells, numbers of lymphocytes, monocytes, granulocytes significantly decreased after adjustment for age, sex, disease	Male lead workers in battery plant in Taiwan (10-20 work-years)	Average BLL = 30 µg/dL	Immune measures in control group, lead-exposed group compared by using multiple linear regression models after adjustment; $p < 0.05$ for circulating monocytes, $CD8^+$ cells.	Relevant to BLL of firing-range instructors.	Kuo et al. 2001

Abbreviations: ALAD, delta-aminolevulinic acid dehydratase; BLL, blood lead level; $CD3^+$, $CD4^+$, $CD8^+$, cluster of differentiation (markers 3, 4, 8); $CD45^+RA^+$, naive memory T cells; CTL, cytotoxic T lymphocytes; HLA, human leukocyte antigen; IgA, IgG, IgE, immunoglobulin A, G, E; IL, interleukin; NKC, natural killer cells; TNF, tumor-necrosis factor; ZPP, zinc protoporphyrin.

in adults who have mean bone lead concentrations over 20 µg/g. Overall, the 2012 report suggested that the available data are sufficient to conclude that there is a causal association between lead exposure and several specific cardiovascular health effects. The report also pointed out that uncertainty exists as to the lead exposure level, timing, frequency, and duration that contribute to the observed associations because the adult populations examined in the epidemiologic research probably had high past lead exposures.

National Toxicology Program 2012 Monograph on Health Effects of Low-Level Lead

The NTP concluded that there is sufficient evidence that BLLs under 10 µg/dL are associated with increased blood pressure and hypertension in adults but that the evidence is limited with respect to associations with cardiovascular-related mortality and other cardiovascular end points, such as ECG conduction abnormalities, heart-rate variability, and clinical cardiovascular diseases. The NTP also indicated that bone lead has been more consistently associated with chronic cardiovascular outcomes, such as hypertension and cardiovascular mortality, than BLL; this suggests that long-term cumulative exposure as measured by bone lead is more critical than concurrent lead exposure reflected by BLLs with regard to chronic cardiovascular outcomes.

Other Studies Considered

Blood Pressure and Hypertension

Two meta-analyses integrated most published studies of the associations of blood pressure and hypertension with BLL and bone lead. Nawrot et al. (2002) examined 31 US and European studies published during 1980-2001 and used the following inclusion criteria: 50 or more subjects, ages 10 years and over, both blood pressure and BLL measurements presented with sufficient detail to estimate the magnitude of the association, and preference given to studies that adjusted for age, body-mass index, and additional factors of proven importance. The meta-analysis, whenever possible, analyzed sex-specific and race-specific associations separately. The combined analysis included 58,518 subjects for systolic blood pressure (SBP) and 58,491 subjects for diastolic blood pressure (DBP). The mean BLL ranged from 2.28 to 63.82 µg/dL (median 12.64 µg/dL; interquartile range 7.46-23.93 µg/dL). The combined overall association sizes for SBP and DBP for each two-fold increase in BLL were 1.0 mm Hg (95% CI: 0.5, 1.4) and 0.6 mm Hg (95% CI: 0.4, 0.8), respectively. Sex differences in the associations of BLL with SBP and DBP were not statistically significant.

Navas-Acien et al. (2008) performed a meta-analysis of the associations of bone lead concentration with blood-pressure outcomes based on three prospec-

tive studies and seven cross-sectional studies published through 2007. The mean tibia lead concentrations ranged from 4.2 μg/g (a study of childhood lead exposure in a lead-smelter cohort in Silver Valley, Idaho, and a nonexposed cohort in Spokane, Washington) (Gerr et al. 2002) to 38.4 μg/g (a study of Korean lead workers) (Glenn et al. 2006), and mean patella lead concentrations ranged from 17.3 μg/g (Boston Nurses Health Study) (Korrick et al. 1999) to 32.1 μg/g (Normative Aging Study) (Hu et al. 1996). The combined summary estimates of SBP and DBP for a 10-μg/g increase in tibia lead were 0.26 mm Hg (95% CI: 0.02, 0.50) and 0.02 mm Hg (95% CI: -0.15, 0.19), respectively. The overall ORs for hypertension were 1.04 (95% CI: 1.01, 1.07) for tibia lead and 1.04 (95% CI: 0.96, 1.12) for patella lead.

Additional individual studies support a possible association of BLL over 10 μg/dL and 40 μg/dL and lower with higher blood pressure. A study in China compared 120 female crystal-toy workers (BLLs of 22.5-99.4 μg/dL) with 70 nonexposed controls (sewing workers, BLLs under 11.4 μg/dL) (Nomiyama et al. 2002). They found that workers who had BLLs of 60 μg/dL or higher had SBP, DBP, and pulse pressure 7.5 mm Hg (95% CI: 3.0, 12.0), 6.3 mm Hg (95% CI: 3.4, 9.1), and 3.4 mm Hg (95% CI: 0.5, 6.2), respectively, higher than those in the control group (BLLs under 11.4 μg/dL).

Glenn et al. (2006) explored whether the association between lead and blood pressure could be an acute response to lead or a long-term cumulative effect of lead. Their cohort consisted of 575 lead-exposed workers in South Korea with a baseline mean (standard deviation [SD]) BLL and tibia bone lead concentration of 31.4 (14.2) μg/dL and 38.4 (42.9) μg/g, respectively. They found that every increase of 10 μg/dL per year in concurrent BLL, as assessed with a longitudinal difference in BLL between visits, was associated with an average annual increase of 0.9 mm Hg (95% CI: 0.1, 1.6) in SBP during the 3-year followup. Tibia lead, however, was nonsignificantly inversely associated with a change in SBP. The authors suggested that SBP might be more responsive to circulating lead (as reflected by BLL), whereas lifetime cumulative dose may influence the risk of hypertension through other biologic pathways. Weaver et al. (2008) also examined the same cohort and observed a statistically significant cross-sectional association of SBP with concurrent BLL but not with patella lead. The significant association remained even after controlling for patella lead. There was no association of DBP or hypertension prevalence with either lead measure. A community-based cohort study conducted in the Baltimore, Maryland, area (Baltimore Memory Study) found that BLL was associated with blood pressure, whereas tibia lead was associated with hypertension; this suggested that "lead has an acute effect on blood pressure via recent dose and a chronic effect on hypertension risk via cumulative dose" (Martin et al. 2006).

Two studies examined BLL and blood pressure by using data from NHANES II. Sorel et al. (1991) reported age-adjusted BLLs of 13.2 μg/dL in black females, 12.1 μg/dL in white females, 20.1 μg/dL in black males, and 16.8 μg/dL in white males. They fitted linear BLL, but Schwartz (1991) constructed a log-linear model (natural log-transformation). Linear BLL was significantly

associated with DBP only in males (β = 0.13 mm Hg; 95% CI: 0.04, 0.21, for every 1 µg/dL) (Sorel et al. 1991), whereas log-linear BLL was significantly associated with DBP in both males (β = 2.93 mm Hg; 95% CI: 0.93, 4.98, for every 1 natural log unit of BLL) and females (β = 1.64 mm Hg; 95% CI: 0.27, 3.01) (Schwartz 1991). Those results suggest that a dose-response relationship between BLL and blood pressure is most likely log-linear.

Clinical Cardiovascular Outcomes

Navas-Acien et al. (2007) conducted a qualitative systematic review of lead exposure and cardiovascular end points except blood pressure and hypertension. They identified 12 studies of clinical cardiovascular end points in general populations and 18 studies of cardiovascular mortality in occupational cohorts. They concluded that the evidence was suggestive but not sufficient to infer causal relationships between lead exposure and clinical cardiovascular outcomes because of the small number of prospective studies, the lack of standardized assessment and information on outcomes, and methodologic limitations, such as exposure and outcome misclassification.

The committee identified one study of an important and specific clinical outcome—incident ischemic heart disease—and four studies of cardiovascular mortality. Jain et al. (2007) examined the association between bone lead and incidence of ischemic heart disease (myocardial infarction or angina pectoris) in a prospective cohort of veterans in the Boston, Massachusetts, area (Normative Aging Study: 83 cases and 754 noncases) with 10 years of followup. The mean (SD) concentrations of baseline BLL, patella lead, and tibia lead were 7.0 (3.8) µg/dL, 36.8 (20.8) µg/g, and 24.2 (15.9) µg/g in cases and 6.2 (4.3) µg/dL, 30.6 (19.7) µg/g, and 21.4 (13.6) µg/g in noncases, respectively. SD increases in BLL and patella lead were significantly associated with a 27% (95% CI of hazard ratio [HR]: 1.01, 1.59) and a 29% (95% CI of HR 1.02, 1.62) increased risk of ischemic heart disease. Compared with subjects who had BLLs under 5 µg/dL, those who had BLLs of 5 µg/dL or higher had an HR of 1.73 (95% CI: 1.05, 2.87). Weisskopf et al. (2009) conducted a survival analysis of mortality in the same cohort (an average of 8.9 years of followup) and found that men in the highest tertile of patella lead had HRs of 2.52 (95% CI: 1.17, 5.41) for all causes, 5.63 (95% CI: 1.73, 18.3) for cardiovascular disease, and 8.37 (95% CI: 1.29, 54.4) for ischemic heart disease. Baseline BLLs were not associated with cardiovascular mortality.

The committee identified other important studies. A study that used data from NHANES II reported a rate ratio of 1.39 (95% CI: 1.01, 1.91) for circulatory mortality associated with BLLs of 20-29 µg/dL compared with BLLs under 10 µg/dL (Lustberg and Silbergeld 2002). Lin et al. (2011) followed 927 dialysis patients in Taiwan for 18 months and found that after adjustment for confounders the upper two tertiles of BLLs (8.51-12.64 µg/dL and over 12.64 µg/dL) were associated with HRs of 3.70 (95% CI: 2.06, 6.48) and 9.71 (95% CI: 2.11,

23.26) compared with the first tertile (BLLs under 8.51 µg/dL). Khalil et al. (2009b) investigated a prospective cohort of 533 women in the Study of Osteoporotic Fractures at two US research centers (Baltimore, Maryland, and Monongahela Valley, Pennsylvania). The baseline mean (SD) BLL was 5.3 (2.3) µg/dL (range 1-21 µg/dL). Over 12 years of followup, women who had BLLs of 8 µg/dL or higher (n = 79) had an HR of 3.08 (95% CI: 1.23, 7.70) for coronary heart disease mortality and an HR of 1.78 (95% CI: 0.92, 3.45) for cardiovascular disease mortality compared with women who had BLLs under 8 µg/dL (n = 453). There was no association with stroke (HR = 1.13; 95% CI: 0.34, 3.81). Finally, many occupational-cohort studies published before 2000 examined mortality from stroke by comparing lead-exposed workers with nonexposed controls. The committee did not find the evidence from those studies compelling, because the associations were inconsistent and there was no lead dose assessment (reviewed by Navas-Acien et al. 2007).

Other Cardiovascular End Points, Including Subclinical Measures

As stated above, the NTP (2012) report suggested that the evidence regarding an association of low-level lead exposure with other cardiovascular outcomes, including subclinical measures, was limited. The committee identified 10 studies that examined subclinical measures—such as ventricular function, heart rate variability, and pulse pressure—and homocysteine, a biomarker of cardiovascular and neurodegenerative diseases.

Poręba et al. (2010, 2011a,b,c) published a series of papers that examined ventricular function, pulse pressure, and heart-rate variability by comparing lead-exposed workers and healthy controls in Poland. The average BLLs were 24.0-26.7 µg/dL in lead-exposed workers and 5.4-8.3 µg/dL in the healthy controls. A unit increase in BLL was associated with an increase of 0.02 (standard error [SE] = 0.01) to 0.03 (SE = 0.01) mm Hg in pulse pressure, an indicator of arterial stiffness, and a 13% increase in the odds of left ventricular diastolic dysfunction (95% CI of OR: 1.10, 1.15). They also found significant positive associations between ZPP and left ventricular hypertrophy (OR = 1.32; 95% CI: 1.26, 1.43, for every 1-µg/dL increase in ZPP) and augmentation index (β = 0.215; SE = 0.01). Lead-exposed workers had significantly lower measures of heart-rate variability, especially depressed vagal activity, than healthy controls (for example, root mean square of successive normal sinus RR interval difference [rMSSD] during the day activity hours: 52.94 ± 21.58 ms in copper-smelter workers vs 79.42 ± 31.14 ms; $p < 0.01$).

The committee believed that studies of lead and homocysteine were relevant to its work because of the large literature relating homocysteine to adverse cardiovascular outcomes (Stampfer et al. 1992; Perry et al. 1995; Verhoef et al. 1997; Humphrey et al. 2008). Chia et al. (2007) investigated an association between BLL and plasma homocysteine, a sulfur-containing amino acid and a risk factor for cardiovascular and neurodegenerative diseases (Shea et al. 2002; Martignoni et al. 2007; Blom and Smulders 2011), in 422 lead-exposed workers in

Singapore (159) and Vietnam (263). BLLs ranged from 2 to 66.9 µg/dL with a mean of 22.7 µg/dL. There was a borderline significant association in an analysis that included all subjects: a 1-µg/dL increase in BLLs was associated with a 0.04-µmol/L increase in homocysteine on the log scale (95% CI: -0.001, 0.082). A polynomial plot of BLL and log-transformed homocysteine showed that homocysteine did not increase until 20 µg/dL, and a clear positive dose-response relationship began to be apparent at BLLs above 20 µg/dL. Yakub and Igbal (2010) also examined 872 healthy adults (18-60 years old) in a low-income urban population of Karachi, Pakistan, whose mean (SD) BLL was 11.65 (5.5) µg/dL. Every 1-µg/dL increase in BLL was associated with a 0.09-µmol/L increase in plasma homocysteine. Compared with the first quartile, the upper three quartiles had significantly higher risks of hyperhomocysteinemia (defined as plasma homocysteine concentrations over 15 µmol/L), with ORs of 1.89, 2.21, and 1.69 for quartiles 2, 3, and 4, respectively. A community-based study also reported a significant association between lead exposure and homocysteine despite a mean BLL under 5 µg/dL (Schafer et al. 2005). In a cross-sectional analysis with 1,037 subjects in the Baltimore Memory Study, a 1-µg/dL increase in BLL was associated with a 0.35-µmol/L increase in plasma homocysteine after controlling for important potential confounding variables. However, as might be expected given mechanistic considerations, tibia lead was not associated with homocysteine concentrations.

The lead studies conducted as part of the Normative Aging Study consistently showed associations between bone lead and subclinical measures of cardiovascular disease. The participants in the cohort were veterans who had had military service and thus might have had lead exposure through the use of firearms. In different studies, the average tibia and patella bone lead concentrations in the Normative Aging Study were about 20 and 30 µg/g, respectively. The mean BLLs were about 6 µg/dL. The average age was about 70 years in 2000. The results of the studies suggest that low-level cumulative exposure to lead is associated with cardiac conduction abnormalities cross-sectionally (Cheng et al. 1998) and longitudinally (Eum et al. 2011) and that subjects who have metabolic syndrome may be more susceptible to cumulative lead exposure-related autonomic dysfunctions (Park et al. 2006).

Summary Findings on Cardiovascular Effects

The committee concludes that the evidence is sufficient to infer causal relationships between BLLs under 40 µg/dL, as well as cumulative dose measures, and increased blood pressure, hypertension, cardiovascular mortality, and subclinical cardiovascular outcomes (see Table 4-7). The committee also concludes that the evidence supporting a causal relationship between BLLs under 40 µg/dL and stroke is inconsistent. Those conclusions reinforce the conclusions of the NTP and EPA but suggest that further studies are needed to conclude whether the relationship between lead exposure and stroke is causal.

TABLE 4-7 Key Studies of the Effects of Lead on Cardiovascular Disease

Health Effects	Population Characteristics	Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
Blood pressure or hypertension	Meta-analysis (31 US, European studies published in 1980-2001) (58,518)	Mean BLLs: minimum = 2.28 µg/dL, Q1 (25%) = 7.46 µg/dL, median = 12.64 µg/dL, Q3 (75%) = 23.93 µg/dL, maximum = 63.82 µg/dL	Pooled estimate per doubling of BLL (95% CI): SBP, 1 mm Hg (0.5, 1.4); DBP, 0.6 mm Hg (0.4, 0.8); male SBP, 1.2 mm Hg (0.6, 1.7); DBP, 0.6 mm Hg (0.4, 0.8); female SBP, 0.8 mm Hg (0.2, 1.4); DBP, 0.6 mm Hg (0.3, 0.9).	Most studies included have BLL >10 µg/dL, in both general populations and occupational cohorts.	Nawrot et al. 2002
	Meta-analysis (3 prospective studies, 5 cross-sectional studies, 1996-2007)	Mean (SD) bone lead in Normative Aging Study: tibia, 22 (13) µg/g; patella, 32 (19) µg/g Korean lead workers: tibia, 38 (40) µg/g Baltimore Memory Study: tibia, 18.8 (12.4) µg/g Boston Nurses Health Study: tibia, 13.3 (9) µg/g; patella, 17.3 (10.6) µg/g Postpartum women: tibia, 8.8 (11.4) µg/g; calcaneus, 11 (12) µg/g	For 10-µg/g increase in tibia, cross-sectional increase: SBP, 0.26 mm Hg (95 % CI: 0.02, 0.5); DBP, 0.02 mm Hg (95% CI: -0.15, 0.19). Hypertension: tibia, OR = 1.04 (95% CI: 1.01, 1.07); patella, OR = 1.04 (95% CI: 0.96, 1.12).	Reflecting cumulative exposure; summary estimates between bone lead markers and blood pressure and hypertension.	Navas-Acien et al. 2008
Cardiovascular mortality	868 male veterans in Normative Aging Study, 8.9 (SD = 3.9) y of followup	Baseline tertile of patella lead: low <22, medium 22-35, high >35 µg/g	HR of all CVD mortality = 1.63 (95% CI: 0.51, 5.18) for medium group, 5.63 (95% CI: 1.73, 18.3) for high group compared with low group; HR of ischemic heart disease = 2.99 (95% CI: 0.40, 22.6) for medium group, 8.37 (95% CI: 1.29, 54.4) for high group.	Long-term exposure studies of veterans probably exposed to lead during military service.	Weisskopf et al. 2009

	927 dialysis patients, 18-month followup, Taiwan	Tertile (309 each): low <8.51, medium 8.51-12.64, high >12.64 µg/dL	HR = 3.70 (95% CI: 2.06, 6.48) for medium group, 9.71 (2.11, 23.26) for high group compared with low group.	CVD mortality in susceptible population.	Lin et al. 2011
CHD and stroke mortality	533 women in Study of Osteoporotic Fractures, 12 y of followup	Baseline BLL = 5.3 (2.3) µg/dL (range 1-21 µg/dL)	BLL ≥ 8 vs <8 µg/dL; CVD HR = 1.78 (95% CI: 0.92, 3.45); CHD HR = 3.08 (95% CI: 1.23, 7.70); stroke HR = 1.13 (95% CI: 0.34, 3.81).	Long-term followup study with wide range of BLLs in women.	Khalil et al. 2009b
Ischemic heart disease	550 male veterans in Normative Aging Study (837 included for blood lead), 10 y of followup	Baseline bone lead levels (SD): noncases (n = 487), tibia = 21.4 (13.6) µg/g, patella = 30.6 (19.7) µg/g; cases (n = 63), tibia = 24.2 (15.9) µg/g; patella = 36.8 (20.8) µg/g	Per 1 SD increase in lead marker: tibia, HR = 1.84 (95% CI: 0.57, 5.90); patella, HR = 2.64 (95% CI: 1.09, 6.37).	Long-term exposure studies of veterans probably exposed to lead during military service.	Jain et al. 2007
Clinical, subclinical CV end points	Systematic review (publications through August 2006): clinical (n = 30), intermediate CV end points (n = 32)	Various ranges	Suggestive but insufficient to conclude causal relationship of lead exposure and clinical CVD outcomes and heart-rate variability.	Integrated review.	Navas-Acien et al. 2007

Abbreviations: BLL, blood lead level; CI, confidence interval; CHD, coronary heart disease; CV, cardiovascular; CVD: cardiovascular disease; DBP, diastolic blood pressure; HR, hazard ratio; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation.

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5

Cancer Effects

On the basis of nonhuman experimental evidence, lead and lead compounds have been recognized as probably or likely to be carcinogenic in humans by several authoritative organizations, including the International Agency for Research on Cancer (IARC 2006), the National Toxicology Program (NTP 2004, 2011), and the US Environmental Protection Agency (EPA 2012). In this chapter, in addition to human studies, the committee relied on evidence from animal cancer bioassays and mechanistic studies in evaluating the evidence supporting a causal link between lead and cancer, as has been done by IARC, NTP, and EPA. Several lead compounds have been used in animal and mechanistic studies, but the committee considered all inorganic forms of lead to be applicable to this review.

A number of animal experiments have demonstrated the carcinogenicity of inorganic lead, mostly in the kidney (renal-cell carcinoma), but cancer at other sites has been reported, including brain tumors (gliomas), lung cancer, and cancers of the hematopoietic system. Lead also has genotoxic potential. Relatively low concentrations of lead in vitro (less than 1 μM) have caused mutations in mammalian cells in a dose-dependent manner, possibly through the generation of reactive oxygen species. Lead inhibits the repair of DNA damage caused by ultraviolet light and x rays and so potentially increases the genotoxicity of other agents. It stimulates lipid peroxidation and may increase free radicals through its inhibition of the enzyme delta-aminolevulinic acid dehydratase (ALAD). Lead also induces micronuclei and increases chromosomal aberrations in mammalian studies, although typically at higher doses than in occupational studies. In addition to genotoxicity, lead increases cell proliferation in the absence of cytotoxicity (IARC 2006). Thus, lead may contribute to carcinogenicity through a variety of mechanisms.

The committee reviewed the human, animal, and mechanistic evidence on lead carcinogenicity, first by the reviewing the evaluations of IARC (2006), NTP (2011), and EPA (2012). The NTP *Monograph on Health Effects of Low-Level Lead* (NTP 2012) reviewed in Chapter 4 did not include cancer end points. Through literature searches, the committee also identified relevant recent studies

not included in the IARC, NTP, or EPA evaluations. Studies of particular relevance in evaluating cancer risks to Department of Defense (DOD) personnel on firing ranges are highlighted below.

CONCLUSIONS FROM THE 2006 INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, 2011 NATIONAL TOXICOLOGY PROGRAM, AND 2012 ENVIRONMENTAL PROTECTION AGENCY REPORTS

International Agency for Research on Cancer 2006 Monograph

On the basis of sufficient evidence from experimental animal studies and limited evidence on humans, IARC (2006) classified inorganic lead compounds as "probably carcinogenic to humans" (Group 2A). The evidence presented in the IARC report consisted of results of human studies of exposed workers and environmentally exposed groups, results of experimental animal studies, and other relevant data. Except for two studies of the second National Health and Nutrition Examination Survey (NHANES II), human studies have relied primarily on comparisons of exposed workers who had blood lead levels (BLLs) mostly over 40 μg/dL. Those studies provided evidence of "no or a slight excess of lung cancer", a 30-50% excess risk of stomach cancer, a two-fold increase in renal cancer, and a risk of glioma. One concern regarding the stomach-cancer findings was the use of external referent populations and the potential differences in dietary habits and *Helicobacter pylori* prevalence (see also Ward et al. 2010). Because of the crude exposure classification used in the studies and because effects of confounding could not be ruled out, IARC did not conclude the epidemiologic evidence sufficient to support a causal association. Instead, IARC found that "there is *limited evidence* in humans for the carcinogenicity of inorganic lead compounds" (IARC 2006, p. 377). However, IARC found the evidence from animal studies sufficient for lead acetate, lead subacetate, lead chromate, and lead phosphate and noted that "extensive experimental evidence shows that various water-soluble and insoluble lead compounds can induce kidney tumours in rodents" and that a study showed they "can occur in the absence of lead-induced nephropathy" (p. 374). It further highlighted the ability of lead to be an effective promoter of organic renal carcinogens.

National Toxicology Program 2011 Report on Carcinogens

The 2004 and 2011 editions of the NTP *Report on Carcinogens* list lead and lead compounds as "reasonably anticipated to be human carcinogens" (NTP 2011, p. 251). The document supporting the NTP deliberation is the *Report on Carcinogens Background Document for Lead and Lead Compounds* (NTP 2003). NTP concluded that the epidemiologic evidence linking cancer with lead was strongest for lung and stomach cancer. It noted, however, that evidence

from human studies was limited by the crude measures of exposure and had the disadvantage of inadequate control for confounding variables (smoking in the case of lung cancer and *H. pylori* infections and socioeconomic status in the case of stomach cancer) and for coexposure to arsenic. NTP's overall "reasonably anticipated" finding was based on animal evidence; it noted that lead compounds caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. NTP noted that benign and malignant renal tumors were most frequently associated with lead exposure and that brain tumors (gliomas), lung cancer, and cancers of the hematopoietic system were also seen in some studies. It emphasized the experiment in mice that showed that gestational and postpartum exposure of dams produced renal lesions, including adenocarcinomas, in offspring. Although the overall conclusion was that the mechanisms by which lead causes cancer were not understood, NTP noted that lead compounds can cause genetic damage through several mechanisms, including inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor-suppressor proteins.

Environmental Protection Agency 2012 Integrated Science Assessment for Lead (Second External Review Draft)

The EPA (2012) *Integrated Science Assessment for Lead (Second External Review Draft)* notes that there is "likely a causal relationship" between lead exposures and cancer. Studies highlighted by EPA included ones that had not been included in its 2006 air quality criteria document for lead and emphasized studies of overall cancer mortality and lung, brain, breast, renal, and other cancers. Human evidence on cancer mortality was found to be mixed, including results from more recent studies of lung cancer. Brain-cancer studies demonstrated stronger effects among particular genotypes. EPA reviewed hypothesis-generating studies in which biomonitored concentrations of lead in urine, blood, or tissue in people that did or did not have particular types of cancer were compared. For example, lead concentrations were highest in tissues adjacent to renal tumors and were higher in cases than in controls (Cerulli et al. 2006). However, a number of limitations were noted in the studies. Similarly, human evidence on other cancers was found to be weak or inconsistent with earlier findings. Nevertheless, findings from mechanistic studies and animal studies were found to be strongly supportive of the carcinogenic potential of lead.

OTHER STUDIES CONSIDERED

Epidemiology Studies

Table 5-1 presents the occupational and environmental epidemiologic studies that the committee believed to be most relevant for evaluating cancer risks posed by lead on DOD firing ranges.

TABLE 5-1 Key Human Studies of the Carcinogenic Effects of Lead

Cancer Type	Population Characteristics	BLL or Other Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
Overall cancer mortality	NHANES II, mortality study (n = 3,592), 203 cancer deaths, average 13.3 y of followup	≤9.8 µg /dL 9.9-12.9 µg/dL 13.0-16.9 µg/dL ≥17.0 µg/dL	Reference RR = 1.24 (95% CI: 0.66, 2.33) RR = 1.33 (95% CI: 0.57, 3.09) RR = 1.50 (95% CI: 0.75, 3.01) p trend = 0.16.	Measured BLL in range lower than current OSHA standard, but higher than current population level	Jemal et al. 2002
	NHANES III, mortality study (n = 9,757), 1988-1994	<5 µg/dL 5-9 µg/dL ≥10 µg/dL	Reference RR = 1.44 (95% CI: 1.12, 1.86) RR = 1.69 (95% CI: 1.14, 2.52) p trend <0.01.	Measured BLL.	Schober et al. 2006
	NHANES III, using data with BLL <10 µg/dL	≤1.93 µg/dL 1.94-3.62 µg/dL ≥3.63 µg/dL	HR = 1.00 HR = 0.72 (95% CI: 0.46, 1.12) HR = 1.10 (95% CI: 0.82, 1.47) p trend = 0.101	—	Menke et al. (2006)
	Normative Aging Study (n = 868)	—	No association with cancer mortality.	Bone lead exposure was measured cumulatively.	Weisskopf et al. 2009
	Women (65-87 y old) enrolled in Study of Osteoporotic Fractures in two US research centers (n = 533)	<8 µg/dL or ≥8 µg/dL	No association with cancer mortality.	—	Khalil et al. 2009
	Male (n = 1,423) and female (n = 3,102) printing-industry workers	—	Pancreatic-cancer mortality (SMR = 2.3; 95% CI: 1.46, 3.68)	No confounding by other workplace carcinogens.	Ilychova and Zaridze 2012
Renal cancer	Nested case-control study of male smokers in Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	<2.50 µg/dL 2.50-3.31 µg/dL 3.31-4.66 µg/dL >4.66 µg/dL	Renal-cell carcinoma: Reference OR = 1.1 (95% CI: 0.6, 2.0) OR = 1.8 (95% CI: 1.0, 3.6) OR = 2.0 (95% CI: 1.0, 3.9) p trend = 0.022	Measured BLL within range of interest.	Southard et al. 2012

	Hospital-based study in Czech Republic, Poland, Romania, Russia (1,097 renal-cell carcinoma cases, 1,476 controls)	Exposure assessed through occupational questionnaires and job exposure matrix, compared exposed vs unexposed	OR = 1.55 (95% CI: 1.09, 2.21)	Adjusted for multiple confounders, including other metals.	Boffetta et al. 2011; van Bemmel et al. 2011 identified variations in risk by ALAD genotype
	Male (n = 1,423) and female (n = 3,102) printing-industry workers	—	Renal-cancer mortality (SMR = 2.2; 95% CI: 1.1, 4.07)	No identified confounding by other workplace carcinogens.	Ilychova and Zaridze 2012
Lung cancer	Lead-only smelter workers (n = 1,992) compared with "unexposed" population	CBLI (for example, 10 µmol/L = average of 1 µmol/L for 10 y or 0.5 µmol/L for 20 y) 2-10 µmol/L (2 µmol/L = 41.6 µg/dL; 10 µmol/L = 208 mg/dL) >10 µmol/L	SIR = 4.5 (95% CI: 1.8, 9.3) SIR = 5.1 (95% CI: 2.0, 10.5)	Measured CBLI; assumed 15-y latent period.	Lundstrom et al. 1997
	Meta-analysis of occupationally exposed battery, smelter workers	BLL mostly >40 µg/dL (if reported) Referent is regional rates	RR = 1.14 (95% CI: 1.04, 1.25)	—	Steenland and Boffetta 2000
	Population-based case-control study in Montreal, Canada (857 cases, 533 controls)	Inorganic lead exposure compared with no exposure Lead exposure from gasoline emissions compared with no exposure	OR = 1.1 (95% CI: 0.7, 1.7) OR = 0.8 (95% CI: 0.6, 1.1)	Adjusted for age, yearly income, cultural origin, proxy status, smoking, occupational exposure to asbestos, silica, arsenic, cadmium, and chromium.	Rousseau et al. 2007

(Continued)

TABLE 5-1 Continued

Cancer Type	Population Characteristics	BLL or Other Measures	Effect Estimate	Why Study Is Relevant to DOD	Reference
	1,462 male tin-smelter workers	Personnel record cards and air Sampling conducted 1972-1991	RR = 1.54 (90% CI: 1.14, 2.08); lead exposure weighted by age and time since exposure.	—	Jones et al. 2007
	Primary smelter workers (46 cases, 141 age-matched controls)	Median CBLI: 9.0 μmol/L for cases, 11.9 μmol/L for controls	OR = 0.99 (95% CI: 0.96, 1.02) per μmol/L.	—	Lundstrom et al. 2006
Brain, nervous system cancer	Occupationally exposed cohort in Finland (10 cases, 50 controls)	CBLI: 01-6 μmol/L 7-14 μmol/L ≥15 μmol/L	Reference OR = 2 OR = 6.2 OR = 12 p trend = 0.02	Measured CBLI.	Anttila et al. 1996
	US-based population, National Longitudinal Mortality Study	Job exposure matrix	Brain-cancer mortality HR = 2.3 (95% CI: 1.3, 4.2) for high probability and intensity of exposure vs unexposed.	US population, supports findings of Anttila et al. (1996).	van Wijngaarden and Dosemeci 2006
	Brain-cancer incident cases from Taiwan National Cancer Registry	Ecologic exposure measure; high, medium, low, or small PLEA	Increase in standardized incidence rate per 100,000 compared with small PLEA (SE): 0.144 (0.148) for low, 0.316 (0.159) for medium, 0.474 (0.186) for high.	—	Wu et al. 2012
	Hospital-based case-control study (55 patients with glioma, 151 with meningioma, 505 controls)	Expert-derived exposure estimate; mean (SD) glioma, 70.5 (193.8) $\mu g/m^3$-y; glioblastoma multiform, 97.5 (233.9) m^3-y; meningioma, 101.1 (408.7) m^3-y; controls, 69.7 (248.8) m^3-y	OR per 100 $\mu g/m^3$-y increase in cumulative lead exposure: glioma, 1.0 (95% CI: 0.9, 1.1); glioblastoma multiform, 1.0 (95% CI: 0.9, 1.1); meningioma, 1.1 (95% CI: 1.0, 1.2).	—	Bhatti et al. 2009

	Hospital-based case-control study (489 patients with glioma, 197 with meningioma, 799 noncancer controls)	Among those with *ALAD*[2] variant allele and cumulative lead exposures of: 1-49 µg/m^3-y, 50-99 µg/m^3-y, ≥100 µg/m^3-y compared with unexposed	Meningioma: OR = 1.1 (95% CI: 0.3, 4.5) OR = 5.6 (95% CI: 0.7, 45.5) OR = 12.8 (95% CI: 1.4, 120.8) Two-sided p trend = 0.06. No associations for glioma.	—	Rajaraman et al. 2006
Liver cancer	Australian male lead workers; referent is regional rates	Workers vs population	SIR = 217 (95% CI: 103, 454).	—	Gwini et al. 2012
Stomach cancer	Meta-analysis of occupationally exposed battery and smelter workers	BLL mostly >40 µg/dL (if reported) Referent is regional rates	RR = 1.34 (95% CI: 1.14, 1.57).	—	Steenland and Boffetta (2000)
Esophageal cancer	Australian male lead workers; referent is regional rates	Workers vs population Workers with BLLs >30 µg/dL vs population	SIR = 240 (95% CI: 129, 447) for all workers SIR = 755 (95% CI: 314, 1,813) for workers with BLL >30 µg/dL.	—	Gwini et al. 2012

Abbreviations: ALAD, delta-aminolevulinic acid dehydratase; CBLI, cumulative blood lead index; HR, hazard ratio; NHANES, National Health and Nutrition Examination Survey (II = second survey, III = third survey); OR, odds ratio; OSHA, Occupational Safety and Health Administration; PLEA, petrol-lead emission area; RR, relative risk; SE, standard error; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

Overall Cancer Mortality

EPA (2012) reported on studies of associations between BLL and overall cancer mortality. Because cancer is a collection of diseases only some of which may be influenced by a particular environmental agent, this approach tends to bias findings toward the null. Studies of the association between BLL and overall cancer mortality are equivocal: few studies support the link between lead exposure and mortality, and many do not. A study of the NHANES III population, for which subjects were matched to the National Death Index, reported that those who had BLLs at a baseline of 5-10 µg/dL were 1.44 times as likely to die from cancer-related causes (95% confidence interval [CI]: 1.12, 1.86) as those who had BLLs under 5 µg/dL, and those who had BLLs of 10 µg/dL or higher were 1.69 times as likely to die from cancer-related causes (95% CI: 1.14, 2.52) as the referent group (Schober et al. 2006). Although the study adjusted for important confounders, such as smoking, it did not consider exposure to other known carcinogens, such as arsenic, which may correlate with lead exposure in the general population. A study of the same population but restricted to subjects who had BLLs under 10 µg/dL found no significant association (Menke et al. 2006); by design, this study had lower statistical power because of a reduced sample size and reduced exposure range. Similarly, a study that used the NHANES II population did not find statistically significant associations, although a weak trend between lead exposure and mortality was reported (Jemal et al. 2002). Studies of other populations have yielded negative findings. The study by Weisskopf et al. (2009), which used the Normative Aging Study population, found no association between lead exposure and cancer mortality, even when bone lead concentration was used as a measure of cumulative exposure. It is possible that the Weisskopf et al. study was subject to survivor bias if those who had the highest exposures died before the bone lead evaluations or if only the healthiest among those who had the highest exposures survived. Finally, a study by Khalil et al. (2009) did not find an association between lead exposure and mortality when it used data on women (65-87 years old) enrolled in the Study of Osteoporotic Fractures. Although the aforementioned studies have the weakness of using overall cancer mortality as the end point, which means that deaths from cancers that may be affected by lead exposure are combined with deaths from cancers that are not so affected, they have the strength of adjusting for several confounders, given their population-based nature (in contrast with studies of workers only).

Cancer-mortality studies of specific cancer types have greater relevance because the measures of effect in potentially affected sites are not diluted by those in unaffected sites. A recent study focused on mortality from specific cancer types found significant associations with lead exposure. Ilychova and Zaridze (2012) reported that risk of renal-cancer and pancreatic-cancer mortality had a two-fold increase (standardized mortality ratio [SMR] for renal cancer = 2.2, 95% CI: 1.1, 4.07; SMR for pancreatic cancer = 2.3, 95% CI: 1.46, 3.68) in

exposed workers compared with the referent population Although studies that compared exposed workers with the referent population are typically confounded by other work-related exposures, the study authors note that this particular study of printing workers was not subject to such bias in that the major work exposure was to lead and no other carcinogens (such as organic solvents) were used in the workplace.

Renal Cancer

Studies of the association between lead and renal cancer were noted in the IARC and NTP evaluations. Evidence of lead effects on renal cancers has been growing in the last decade, and a recent well-conducted study has added supporting evidence of the link. Using data from a nested case-control study of male smokers in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Southard et al. (2012) estimated a two-fold increase in the odds of renal cancer (95% CI: 1.0, 3.9) when comparing the 4th quartile (over 4.6 µg/dL) with the 1st quartile (under 2.5 µg/dL) of BLL at baseline. Cases included subjects wo had a diagnosis of renal-cell carcinoma at least 5 years after enrollment and at least 2 months after whole-blood draw. Controls were matched on age at randomization (± 7 years), whole-blood draw date (± 20 days in the same season), pack-years of smoking, and time to followup. In their case-control study, Boffetta et al. (2011) also showed an increased risk in those who were ever occupationally exposed to lead compared with unexposed subjects (OR = 1.55; 95% CI: 1.09, 2.21). Strengths of the study included adjustment for other metals and confounders. The association between lead exposure and renal-cancer mortality previously mentioned (Ilychova and Zaridze 2012) also supports an association between lead and renal cancer; the risk was two-fold greater (SMR = 2.2; 95% CI: 1.1, 4.07) in printing workers as in the referent population.

Lung Cancer

Evidence of links between lead exposure and lung cancer relies on studies that compared exposed workers with a referent population (based on either country or regional cancer rates). In a meta-analysis of eight studies that compared exposed workers with their referent populations, Steenland and Boffetta (2000) found an association between lead exposure and lung cancer. In six of the eight studies, the average BLLs of exposed workers were over 40µg/dL; one study reported only air concentrations (the geometric mean of respirable dust concentrations measured with personal samplers was 48 µg/m^3). Steenland and Bofetta (2000) estimated a 14% higher cancer risk (meta-analysis relative risk [RR] = 1.14; 95% CI: 1.04, 1.25) in comparing exposed workers with their referent population. The study of Jones et al. (2007) also found an increased risk in exposed workers compared with their referent population (RR = 1.54; 90% CI:

1.14, 2.08). However, those studies controlled inadequately for confounders, such as smoking or asbestos exposure, because information on the unexposed (general) population that served as the comparison group was not available. Another study of occupationally exposed adults compared with their referent populations did not show significant associations between lead exposure and lung cancer (Rousseau et al. 2007) and was able to adjust for important confounders (OR = 1.1; 95% CI: 0.7, 1.7); however, the confidence bounds in this study did not preclude the finding of the degree of association reported by Jones et al. (2007). Although weak in their design, lung-cancer studies lend support to the existence of a link between lead exposure and lung cancer.

Brain and Nervous System Cancers

Since the early study of Anttila et al. (1996) reported a significant association between lead exposure and brain cancers in occupationally exposed workers compared with their referent population, at least six studies have examined this association. van Wijngaarden and Dosemeci (2006) used a job-exposure matrix to classify participants in the National Longitudinal Mortality Study into exposure categories based on intensity and duration. The hazard rate for mortality comparing those with high probability and intensity of exposure with those who were not exposed was 2.3 (95% CI: 1.3, 4.2). On the basis of a case-control study, Rajaraman et al. (2006) found a significant increase in meningioma risk associated with cumulative lead exposure (OR = 12.8; 95% CI: 1.4, 120.8 for highest-exposure group vs a referent group); the association was seen in those with the *ALAD*^{2} allele. The case-control study of Bhatti et al. (2009) also found an increased risk of meningioma (OR = 1.1; 95% CI: 1.0, 1.2). Results of multiple human studies now support a link between lead exposure and nervous system cancers.

Animal Studies

Experiments in rats in the late 1950s and early 1960s found that lead caused renal tumors. Lead salts were and are used to administer lead in animal experiments. Carcinogenesis studies used lead forms of varied solubility, such as lead phosphate (insoluble, +2 valence) and lead subacetate and acetate (soluble, +2 valence), each of which induced renal tumors in animal experiments. Various routes of exposure were used (gavage, drinking water, feed, lactational and placental exposure, injection, and subcutaneous injection). Each of the experiments has limitations—for example, studies often examined only the kidneys)—and none followed the design of the standard carcinogenesis bioassay that is used today by the NTP. Nonetheless, as a whole they demonstrate that lead is a carcinogen in mice and rats. Table 5-2 shows tumor dose-response data on renal tumors in some of the rodent studies.

TABLE 5-2 Dose-Response Data on Renal Tumors from Some Oral Studies in Rodents

Lead Exposure	Study Duration (wk)	Sex	Dose Rates (mg/kg-day)[a]	Tumor Incidence	Reference
Rats					
Lead acetate in drinking water	76	Male	0, 130	0/10, 13/16	Koller et al. 1985
Lead acetate in feed	104	Male	0.12, 0.2, 0.72, 2.5, 5.6, 22, 45, 84	0/20, 0/100, 0/50, 0/50, 0/50, 5/50, 10/20, 16/20	Azar et al. 1973
	104	Female	0.15, 0.25, 0.9, 3.1, 7.1, 27, 56, 105	0/20, 0/100, 0/50, 0/50, 0/50, 0/20, 7/20	
Lead acetate in drinking water	104	Male	0, 2.0, 10, 40	0/55, 0/42, 5/52, 24/41	Fowler and Lipsky 1999
Lead subacetate in feed (low dose)	126	Male	0, 15	0/14, 5/16	van Esch et al. 1962
	126	Female	0, 18	0/15, 6/16	
Lead subacetate in feed (high dose)	104	Male	0, 146	0/13, 6/13	
	104	Female	0, 183	0/13, 7/11	
Lead subacetate in feed	78	Male	0, 146	0/30, 13/29	Kasprzak et al. 1985
Lead subacetate in feed	99	Male	0, 146	1/20, 31/40	Mao and Molnar 1967
Mice					
Lead subacetate in feed	104	Male	0, 44	0/19, 6/20	van Esch and Kroes 1969

[a]Administered concentrations converted to equivalent doses of lead.
Source: Adapted from CalEPA (2002).

Of male Wistar rats that received 1% lead acetate in their diet for 1 year, 88% developed renal carcinoma (Boyland et al. 1962). Another experiment with Wistar rats that were fed lead subacetate in the diet found renal tumors in both the high-dose (1%) and low-dose (0.1%) groups (van Esch et al. 1962). Several later experiments in Wistar rats exposed via the diet to either lead subacetate or lead acetate also observed renal tumors (Mao and Molnar 1967; Zawirska and Medras 1968, 1972; Ito et al. 1971; Ito 1973; Waszynski 1977); many of these included observations of renal carcinoma. Renal tumors were also observed in different rat strains. For example, Sprague Dawley rats that received 1% lead

subacetate in the diet had renal tumors, and the incidence was increased in animals that also received calcium (Kasprzak et al. 1985). In male and female Fischer 344 rats that received lead acetate in the diet (Fears et al. 1989), both sexes were affected; the male was more sensitive. Lead acetate in the diet (1%) induced tumors in male CD Sprague Dawley rats (Oyasu et al. 1970). The latter studies also examined lead in combination with other carcinogens and found no carcinogenic interactions. Drinking-water studies in male Sprague Dawley rats (Koller et al. 1985) and male Fischer rats (Fowler and Lipsky 1999) also observed lead-induced renal tumors.

Renal tumors were induced in two experiments with subcutaneous injection of lead phosphate in albino rats (Zollinger 1953; Balo et al. 1965) and in an experiment that used both subcutaneous and intraperitoneal injection in albino Chester Beatty rats (Roe et al. 1965).

Dietary calcium was observed to increase the effectiveness of lead in drinking water in causing renal tumors in Wistar rats (Bogden et al. 1991). A 1-year inhalation study that included a group of rats that were exposed to lead oxide did not observe lung tumors and found only one treated animal that had a renal tumor (Monchaux et al. 1997). Standard carcinogenicity studies in rats usually have a duration of 2 years, so this shorter study may have precluded the observation of late-occurring tumors. Hyperplastic and squamous metaplastic foci of the alveolar region were found in hamsters that received intratracheal administration of lead oxide, and lead oxide showed a cocarcinogenic effect with benzo[a]pyrene (Kobayashi and Okamoto 1974).

In one study that was not well described (for example, the strain and age of the rats were not provided), groups of 50 rats of each sex were given diets that contained lead acetate at 10, 50, 100, or 500 ppm for 2 years (Azar et al. 1973). Groups of 20 animals that received 1,000 or 2,000 ppm were added in a second experiment. In males, 10% of the animals in the 500-ppm group, 50% in the 1,000-ppm group, and 80% in the 2,000-ppm group developed renal tumors. The 500-ppm group had an average BLL of 77.8 μg/dL.

In mice, renal tumors have been induced by lead acetate in the diet (van Esch and Kroes 1969). A significant dose-related trend in renal proliferative lesions (atypical hyperplasia, adenoma, and adenocarcinoma) was observed in male and female offspring of $B6C3F_1$ mice that were exposed to lead in drinking water while pregnant and after birth (Waalkes et al. 1995).

Renal tumors were not observed in Syrian Golden hamsters that were fed lead acetate for up to 2 years (van Esch and Kroes 1969).

Pulmonary adenomas were induced in Strain A/Strong mice given intraperitoneal injections of lead; kidneys were not examined in these studies (Stoner et al. 1976; Shimkin et al. 1977). In studies in Strain A mice, intraperitoneal injections of lead subacetate increased the incidence of pulmonary tumors (Poirier et al. 1984).

SUMMARY FINDINGS

There is consistent and strong evidence that lead causes benign and malignant renal tumors in animals; tumors at additional sites have also been observed in some animal studies. Findings of renal tumors after exposure by multiple routes suggest that the kidney is a target for any route that results in increased BLLs. The finding of renal cancers in offspring of dams that were exposed to lead raises concerns about exposures of women of reproductive age. Animal studies have not clearly demonstrated lung-cancer risk, but lead exposure by inhalation has been inadequately studied. Mechanistic studies have provided supporting evidence of the potential carcinogenicity of lead. Some studies showed tumor induction at concentrations that were not cytotoxic and thus supported mechanisms at micromolar concentrations. Human studies have provided more limited evidence. Although it was not emphasized in the recent EPA review draft, there is additional epidemiologic evidence on both renal and brain cancers. These conclusions are consistent with the overall conclusions presented in the NTP, IARC, and EPA draft reports.

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6

Conclusions

The Occupational Safety and Health Administration (OSHA) lead standard for general industry applies to US military firing ranges and was the main focus of the committee's effort to determine whether "current exposure standards used at ranges are protective". In addressing its charge, the committee initially evaluated the firing-range environment and associated occupational lead exposures (Chapter 1). Atmospheric lead concentrations collected by the US Army, US Air Force, and US Navy during the last few years showed that mean air lead concentrations on military firing ranges were often above OSHA's current permissible exposure limit (PEL) of 50 $\mu g/m^3$ (8-hour time-weighted average). The committee reviewed the historical development of the current OSHA lead standard (Chapter 2) and the toxicokinetics of lead (Chapter 3) and then considered the adverse health effects of lead with respect to noncancer end points (Chapter 4) and cancer outcomes (Chapter 5).

In this chapter, the committee presents its conclusions as to whether current OSHA exposure standards used on firing ranges are protective. The committee used the following questions to guide the presentation of its conclusions:

- Are OSHA's guidelines for blood lead levels (BLLs) adequate to protect Department of Defense (DOD) firing-range personnel?
- Is the current OSHA PEL adequately protective of DOD firing-range personnel?
- Is the current OSHA action level for medical surveillance appropriate?
- Were data gaps identified in answering the questions above? Is research needed to fill those gaps?

The committee's charge also stated that "information will be evaluated on recurrent lead exposures at such firing ranges, and relevant toxicological and epidemiological information on any carcinogenic and non-carcinogenic effects of exposures to lead will be evaluated. The evaluated information will include reviews by the Environmental Protection Agency [EPA] and the National Toxi-

cology Program [NTP]". In keeping with its charge, the committee initially evaluated key literature presented in the NTP's 2012 *Monograph on Health Effects of Low-level Lead,* the EPA's 2006 *Air Quality Criteria Document [AQCD] for Lead* Final Report, the 2012 EPA's *Integrated Science Assessment for Lead (Second External Review Draft),* the International Agency for Research on Cancer (IARC) monograph *Inorganic and Organic Lead Compounds* (IARC 2006), and the 2004 and 2011 editions of the NTP *Report on Carcinogens*. The committee then considered studies that were not included in those reviews. During this step, the committee gave greater weight to other systematic reviews and studies that included meta-analyses.

The committee used additional considerations to narrow its work. Health-effects data on BLLs below 40 µg/dL were primarily considered because the current OSHA standard aims to maintain BLLs below that concentration. Whenever possible, the committee based its conclusions on occupational and other studies of relevance to DOD personnel that work at firing ranges. Special consideration was given to women who might be pregnant or nursing because of the well-known effects of lead on the developing nervous system. The committee also favored studies that considered potential covariates in their statistical analyses; these included tobacco use, alcohol consumption, and coexposure to other metals and chemicals. The committee's conclusions emphasized outcomes associated with clinical disease rather than early biologic effects. For example, the committee considered decrements in circulating hemoglobin to be more important than increases in zinc protoporphyrin. In reaching its conclusions, the committee considered the weight of evidence and relied most heavily on findings of lead-induced adverse health effects that had been replicated in multiple peer-reviewed studies.

The committee's conclusions are based on noncancer end points. Although IARC, NTP, and EPA have identified lead as probably carcinogenic in humans, such findings were based largely on studies of laboratory animals. The available human studies on cancer were insufficient for the committee to draw a conclusion about BLLs that might be associated with cancer in humans.

ARE OCCUPATIONAL SAFETY AND HEALTH GUIDELINES FOR BLOOD LEAD LEVELS ADEQUATE TO PROTECT DEPARTMENT OF DEFENSE FIRING-RANGE PERSONNEL?

The primary purpose of the Occupational Safety and Health Act (29 USC 655 et seq) is to ensure, to the extent possible, safe and healthful working conditions for every American worker over his or her working lifetime. OSHA's lead standard requires that a worker who has a single BLL over 60 µg/dL or three BLLs averaging over 50 µg/dL be removed from performing lead work until his or her BLL is under 40 µg/dL on two occasions. Thus, the current OSHA lead standard recognizes a level of concern for workers who have BLLs of 40-60 µg/dL or higher. The committee therefore focused its attention on whether lead

exposures that result in BLLs of 40 µg/dL or below could result in material impairment of health or functional capacity in DOD firing-range workers. It is important to note that BLL generally reflects short-latency, acute health effects of recent lead exposure. However, to some extent, BLLs later in life reflect cumulative lead exposure, so the interpretation of studies of BLLs later in life is problematic with regard to defining a "threshold level" for a health effect. The committee also recognized that peak BLLs, average BLLs, and current BLLs could be expected to have different associations with health outcomes, depending on mechanism of action, latency, and other considerations.

The committee concludes that the current OSHA standard of a BLL of under 40 µg/dL is not sufficiently protective of personnel who have repeated lead exposures on firing ranges. The committee concludes that the evidence is sufficient to infer causal relationships between BLLs under 40 µg/dL and impaired neurologic, hematopoietic, renal, reproductive, and cardiovascular function. Examples of acute and chronic adverse health effects that have been reported in the literature and are relevant for DOD firing-range personnel (and their associated mean BLL, benchmark dose, or lowest observed BLLs) are[1]

- Reduced fetal growth and low birth weight (maternal BLL under 5 µg/dL).
- Increased cardiovascular-disease mortality (BLL 8 µg/dL or higher).
- Increased serum creatinine, an indicator of renal injury (BLL 8-12 µg/dL).
- Hearing loss (BLL under 10 µg/dL).
- Increased blood pressure (BLL under 10 µg/dL).
- Preterm birth (BLL under 10 µg/dL; evidence on this level is growing stronger).
- Altered postnatal development and growth (maternal BLL under 10 µg/dL).
- Impaired balance (BLL = 14 µg/dL, identified as a benchmark dose).
- Neuronal loss and myelin alterations (BLL = 16.9 µg/dL).
- Slowed visual evoked potentials (BLL = 17-20 µg/dL).
- Decreased psychomotor speed and dexterity and executive function (BLL = 18 µg/dL).
- Decreased erythrocyte, hematocrit, and hemoglobin concentrations (BLL = 20-30 µg/dL).
- Decreased creatinine clearance and glomerular filtration rate, indicators of renal injury (BLL = 20-30 µg/dL).
- Altered parasympathetic and sympathetic activity (BLL = 20 µg/dL or higher).
- Slowed brainstem auditory evoked potentials (BLL = 26-30 µg/dL).

[1]The reader is referred to Chapter 4 for additional details about individual studies.

- Altered verbal memory and learning and reaction time (BLL = 26-30 μg/dL).
- Changes in electric activity of the brain evidenced by slow alpha rhythm (BLL = 29 μg/dL).
- Altered peripheral sensory nerve function (BLL = 30 μg/dL).
- Increased plasma renin activity, angiotensin, angiotensin-converting enzyme, and aldosterone (BLLs = 30-40 μg/dL; these changes are indicative of alterations in renal endocrine functioning and may be responsible, in part, for the increases in blood pressure observed with high BLLs).

The committee also considered studies that reported an association between cumulative lead dose, as assessed by cumulative blood lead index (CBLI) or bone lead concentration, and adverse health outcomes. Associations of health outcomes with CBLI or tibia lead concentrations are probably representative of longer-latency, chronic health effects of cumulative dose. In considering CBLI and bone lead data, the committee used the following assumptions: a BLL of 40 μg/dL over a 40-y working lifetime would be equivalent to a CBLI of 1,600 μg-years/dL, and this CBLI is roughly equivalent to a bone lead concentration of 40-80 μg/g (on the basis of the published relation that tibia lead can be estimated as 2.5-5% of the CBLI) (Hu et al. 2007; Healey et al. 2008). Thus, the committee examined evidence that suggested whether a CBLI of under 1,600 μg-years/dL or a bone lead concentration of under 40-80 μg/g may be associated with adverse health effects of lead exposure.

Because the current OSHA standard does not address CBLI or bone lead concentrations directly, the committee considered data on this measurement to be supportive evidence for its conclusions. Such data included the following:

- Neuronal loss and myelin alterations of brain measured with magnetic resonance spectroscopy (mean bone lead = 7 μg/g).
- Hypertension (bone lead concentrations of 13-38 μg/g).
- Slow alpha activity on electroencephalogram (mean bone lead = 26 μg/g, mean CBLI = 546 μg-years/dL).
- Increased cardiovascular mortality (bone lead concentration over 35 μg/g).
- Increased incidence of ischemic heart disease (bone lead concentrations over 35 μg/g).
- Decreased hemoglobin and hematocrit (bone lead concentration around 35 μg/g, the difference between the highest and lowest quintiles of bone lead).
- Depression symptoms (mean bone lead = 37 μg/g).
- Altered quantitative sensory function in peripheral nerves (mean bone lead = 37 μg/g, mean CBLI = 546 μg-years/dL).
- Altered psychomotor speed and dexterity (mean bone lead = 38 μg/g).
- Slowed brainstem auditory evoked potentials (mean CBLI = 723-934 μg-years/dL).

- Altered psychomotor speed, dexterity, verbal memory, and executive function (mean CBLI = 765 μg-years/dL).
- White matter change in the brain measured by magnetic resonance imaging (mean bone lead = 39 μg/g, mean CLBI = 826 μg-years/dL).

IS THE CURRENT OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION PERMISSIBLE EXPOSURE LIMIT ADEQUATELY PROTECTIVE OF DEPARTMENT OF DEFENSE FIRING-RANGE PERSONNEL?

The ability to predict BLLs on the basis of air lead concentrations is central to the development of the OSHA standard's PEL. The OSHA PEL of 50 $\mu g/m^3$ was set to result in the average lead worker's having a BLL under 40 μg/dL. That BLL was judged by the committee to be inadequate for protecting personnel who had repeated lead exposures on firing ranges (see response to the first question above); thus, the OSHA PEL for lead would also be insufficiently protective.

The committee was not able to estimate an air lead concentration that would protect firing-range workers from adverse health effects that could occur at BLLs of 40 μg/dL or lower, but a concentration below the current PEL of 50 $\mu g/m^3$ clearly is warranted. As discussed in Chapter 3, the OSHA PEL was based on a model produced by the Massachusetts Institute of Technology Center for Policy Alternatives (CPA) (Ashford et al. 1977). The CPA model relied on data from manufacturing operations that may not be directly relevant to firing-range exposures, including differences in lead aerosol particle size, frequency and duration of exposure, assumptions regarding lung deposition and absorption of inhaled particles, and contributions from routes of exposure other than inhalation.

IS THE CURRENT OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION ACTION LEVEL FOR MEDICAL SURVEILLANCE APPROPRIATE?

The OSHA lead standard also creates an air action level for medical surveillance. If it is determined that airborne lead concentrations exceed the action level for more than 30 days/year, an employer must provide a medical surveillance program that consists of biologic monitoring and medical examinations and consultations. The OSHA action level for airborne lead exposure is 30 $\mu g/m^3$ (8-hour time-weighted average). On the basis of the CPA model (Ashford et al. 1977), that exposure concentration would mean that the average lead worker with 1 year of work experience would have a BLL of about 30 μg/dL. Workers with longer job duration would have higher BLLs. As noted above in response to the first question, BLLs under 30 μg/dL have been linked to renal, neurologic, hematologic, reproductive, cardiovascular, and developmental ef-

fects. Thus, the action level for lead would have to be lowered in conjunction with the PEL if the lower PEL is still deemed insufficient to protect all workers. In setting the action level, consideration should also be given to the contribution of oral (hand-to-mouth) exposure to lead.

WERE DATA GAPS IDENTIFIED IN ANSWERING THE QUESTIONS ABOVE? IS RESEARCH NEEDED TO FILL THOSE GAPS?

The committee did not identify any data gaps that threatened its confidence in answering the questions above. However, several data gaps on related subjects were identified during the committee's deliberations, including the following:

- Epidemiology studies of firing-range personnel are few.
- To the committee's knowledge, size distribution and chemical speciation of airborne lead particles associated with firing ranges have not been performed. Such information could be used to estimate the bioavailability of the lead particles found in firing-range air.
- The CPA model used in the OSHA standard to predict BLLs from air lead concentrations may not be appropriate for direct application to firing-range personnel, so physiologically based pharmacokinetic or other dosimetry models may need to be developed for this purpose. Those models could consider other biometrics of exposure, such as bone and semen lead levels.
- The extent to which occupational oral exposure to lead-based dusts found in the firing-range environment by hand-to-mouth contact contributes to total lead body burden has not been adequately characterized.
- The immunotoxicity of low-level lead exposure has been incompletely studied in adults.
- Interactions between noise and lead exposure have been incompletely evaluated.

POTENTIAL RISK-ASSESSMENT OPTIONS

Many groups have proposed alternative management guidelines for BLLs. Most recently, an expert group recommended that BLLs be kept below 20 μg/dL to prevent the acute effects of recent doses (Schwartz and Hu 2007), and this has been supported by the American College of Occupational and Environmental Medicine (ACOEM 2010). For the prevention of the chronic health effects of cumulative doses, the group recommended that tibia lead levels not be allowed to exceed 15 μg/g; this could be achieved, for example, by keeping the average BLL below 10 μg/dL for 40 y (Hu et al. 2007; Schwartz and Hu 2007).

Professional organizations—such as ACOEM, the Association of Occupational and Environmental Clinics (AOEC), and the Council of State and Territorial Epidemiologists (CSTE)—have called for more protective guidelines. For

example, ACOEM (2010) has recommended medical removal of workers who have BLLs of 20 µg/dL or higher. AOEC (2007) has recommended more stringent guidelines for medical management of lead-exposed workers, which have been incorporated into DOD's guidance for occupational medical examinations and surveillance (DOD 2007). CSTE (2009) has recommended that the case definition of *elevated* BLLs in adults be changed from 25 µg/dL to 10 µg/dL. All those organizations recommend that BLLs be kept under 5 µg/dL in pregnant women to reduce the risk of spontaneous abortion.

The US Centers for Disease Control and Prevention (CDC) has developed guidelines that recommend followup activities and interventions beginning at a BLL of 5 µg/dL in pregnant women (CDC 2010) and children (CDC 2012). That BLL is not a "level of concern" or an allowable exposure but rather a level at which it may be prudent to initiate testing and interventions to reduce lead exposure. CDC found convincing evidence that prenatal lead exposure impairs children's neurodevelopment and so places them at increased risk for developmental delay, reduced IQ, and behavioral problems (CDC 2010). The committee agrees that there is a need for additional protection of women of childbearing age, especially pregnant and lactating women.

ADDITIONAL CONSIDERATIONS

It was unclear to the committee what the potential health risks to DOD firing-range personnel might be, because BLL data specifically on DOD firing-range workers were limited. However, data on airborne concentrations of lead on DOD firing ranges indicate that the current OSHA PEL is exceeded in the performance of some job duties—in some cases by several orders of magnitude. Thus, DOD should consider analyzing BLLs of a representative sample of firing-range workers in all the services and comparing them with BLLs linked to adverse health outcomes so that it can understand potential risks and guide risk-management decisions regarding its ranges. Consideration should be given to risk analyses of available control options to determine how to minimize exposure to lead. Control options that could be explored in such analyses include the following:

- *Ammunition substitution*. Exposure of shooters to airborne lead might be reduced by replacing traditional lead bullets with nylon-clad, copper-jacketed, zinc-based, or other forms of ammunition. However, the committee recognizes that training requirements may limit the use of those forms of ammunition and that the use of jacketed and other alternative bullets may entail increased cost.
- *Continuing improvement in range design and ventilation*. The committee recognizes that some modifications may be difficult to implement, particularly as "retrofits" of existing ranges, and that high-efficiency ventilation is expensive to install and operate.

- *Range cleaning*. Scott et al. (2012) found that although ventilation is important for controlling lead exposures, housekeeping can also have a substantial effect on lead contamination on surfaces on and around a shooting range. Even on ranges that have good ventilation and that use ammunition with lead-free primers, poor housekeeping or failing to decontaminate a range thoroughly before switching primers may adversely affect lead exposures.

The Navy Environmental Health Center notes, in its *Indoor Firing Ranges Industrial Hygiene Technical Guide* (NEHC 2002), that although there are no established limits for surface lead contamination in workplaces, OSHA (1993) has indicated in a compliance instruction for the construction industry (CPL 2-2.58) that an acceptable lead loading for nonlead work areas should be 200 $\mu g/ft^2$. Appendix D of the technical guide suggests clearance levels of 200 $\mu g/ft^2$ for interior floors and horizontal surfaces and 800 $\mu g/ft^2$ for exterior concrete.

- *Hygiene practices*. Strict adherence to the OSHA lead-standard recommendations for personal hygiene is critical, and additional hygiene practices should also be considered. Sato and Yano (2006) detected lead contamination on the hands of lead-handling workers at a battery-recycling plant even after workers had washed their hands or bathed. More recent investigations have demonstrated that washing with soap and water is not effective in removing lead from skin. Esswein et al. (2011) found that hand decontamination, rather than washing, is required to ensure complete removal of lead. A mixture of isostearamidopropyl morpholine lactate and citric acid applied with a textured absorbent material was almost 100% effective in removing lead from skin. They suggest that the best method for preventing hand-to-mouth exposure to lead may be skin decontamination and a colorimetric method to detect remaining contamination.

If DOD's occupational exposure limit for lead is lowered, surface and skin decontamination is likely to play an even more important role in effective control of employee exposures than in the past. It will be important for updated guidelines to address the importance of decontamination in more detail and with greater precision. When possible, quantitative levels of contamination should be included in the guidelines rather than qualitative statements regarding the importance of housekeeping.

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Appendix

Biographic Information on the Committee on Potential Health Risks from Recurrent Lead Exposure of DoD Firing Range Personnel

David C. Dorman (*Chair*) is professor of toxicology in the Department of Molecular Biosciences of North Carolina State University. His research is directed toward understanding human health risks associated with environmentally relevant chemicals. It is focused primarily on the respiratory toxicology, neurotoxicology, and pharmacokinetics of environmental agents. He has served on several National Research Council committees, including serving as chair of the Committee on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants and as a member of the Committee to Review the Draft IRIS Assessment on Formaldehyde. Dr. Dorman received his DVM from Colorado State University and his PhD in veterinary biosciences and toxicology from the University of Illinois at Urbana–Champaign. He is a diplomate of the American Board of Veterinary Toxicology and of the American Board of Toxicology and a fellow of the Academy of Toxicological Sciences.

Susan H. Benoff was formerly director of the Fertility Research Laboratories of the Feinstein Institute for Medical Research. She was also an associate professor in the Department of Obstetrics and Gynecology of New York University School of Medicine and director of the Molecular Biology Laboratories, Division of Human Reproduction, in the Department of Obstetrics and Gynecology of North Shore University Hospital. Her research interests were in male infertility and testicular cancer with emphasis on the role that environmental exposure to heavy metals and compounds with hormone-like activity may play in the causes of these disorders. She has been an active member of the American Society for Reproductive Medicine, most recently serving as chair of the Environment and Reproduction Special Interest Group. She is also on the Board of Di-

rectors of the Society for Male Reproduction and Urology and a member of the Council of the American Society of Andrology. Dr. Benoff received her PhD in cell biology from the Albert Einstein College of Medicine of Yeshiva University.

Edward C. Bishop was formerly vice president of Parsons Government Services. He has diverse experience in industrial hygiene, environmental compliance, emergency response, and risk assessment. He had a 20-year career in the US Air Force, in which he held a number of positions, including senior bioenvironmental engineering program manager in the Office of the Air Force Surgeon General. In that position, he developed and managed occupational-health, industrial-hygiene, and environmental-protection programs worldwide. Dr. Bishop has served on several National Research Council committees, including the Committee on Acute Exposure Guideline Levels and the Committee on Toxicological Risks to Deployed Military Personnel. He received his MS in engineering from the University of California, Los Angeles, and his PhD in environmental health sciences from the University of California, Berkeley.

Margit L. Bleecker is director of the Center for Occupational and Environmental Neurology in Baltimore, Maryland. Her research interests are in clinical industrial neurotoxicology and occupational neurology. Dr. Bleecker was a member of the National Research Council Committee on Tetrachloroethylene and the Institute of Medicine Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides and Committee on the DOD Persian Gulf Syndrome Comprehensive Clinical Evaluation Program. She received her PhD from the State University of New York Downstate Medical Center and her MD from the University of California, San Francisco, School of Medicine. Dr. Bleecker is certified by the American Board of Psychiatry and Neurology.

Lisa M. Brosseau is associate professor in the Division of Environmental and Occupational Health Sciences of the University of Minnesota School of Public Health. Her research interests are in the performance of respiratory protection devices, aerosol measurement, filtration, and health and safety interventions. Dr. Brosseau is a former chair of ACGIH's Chemical Substances Threshold Limit Value Committee and past chair of the organization's Board of Directors. She has been on several National Research Council committees, including the Committee on Full System Testing and Evaluation of Personal Protection Equipment Ensembles in Simulated Chemical and Biological Warfare Environments. She received her MS and ScD in industrial hygiene from Harvard University and is certified by the American Board of Industrial Hygiene.

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Judith T. Zelikoff is a professor in the Department of Environmental Medicine of the New York University Medical Center. Her research interests are in immunotoxicity and reproductive and developmental toxicity associated with inhaled metal oxide nanomaterials, respirable particulate matter, and metal-bearing air-pollution mixtures. She is on the National Toxicology Program Board of Scientific Councilors and is an active member of the Society of Toxicology; she was president of the Metals Specialty Section and of the Immunotoxicity Specialty Section and currently serves on the Board of Councilors and is the secretary-elect of the society. Dr. Zelikoff was a member of the National Research Council Committee on Spacecraft Exposure Guidelines. She received her MS in microbiology and her PhD in experimental pathology from the University of Medicine and Dentistry of New Jersey.