Humans live in a chemical environment and inhale, ingest, or absorb from the skin many of these chemicals. Toxicology is concerned with the deleterious effects of these chemical agents on all living systems. In the biomedical area, however, the toxicologist is primarily concerned with adverse effects in humans resulting from exposure to drugs and other chemicals as well as the demonstration of safety or hazard associated with their use.

**Occupational Toxicology**

 Occupational toxicology deals with the chemicals found in the workplace. The major emphasis of occupational toxicology is to identify the agents of concern, identify the acute and chronic diseases that they cause, define the conditions under which they may be used safely, and prevent absorption of harmful amounts of these chemicals. Occupational toxicologists may also define and carry out programs for the surveillance of exposed workers and the environment in which they work. Regulatory limits and voluntary guidelines have been elaborated to establish safe ambient air concentrations for many chemicals found in the workplace.

Governmental and supra governmental bodies throughout the world have generated workplace health and safety rules, including short-and long-term exposure limits for workers. Copies of the United States Mine Safety and Health Administration (MSHA) standards may be found at http://www.msha.gov . Voluntary organizations, such as the American Conference of Governmental Industrial Hygienists (ACGIH), periodically prepare lists of recommended threshold limit values (TLVs) for many chemicals. These guidelines are periodically updated, but regulatory imperatives in the United States are not updated except under certain extraordinary circumstances. These TLV guidelines are useful as reference points in the evaluation of potential workplace exposures. Copies of current TLV lists may be obtained from the ACGIH at h ttp://www.acgih.org.

 **Environmental Toxicology**

 Environmental toxicology deals with the potentially deleterious impact of chemicals, present as pollutants of the environment, on living organisms. The term environment includes all the surroundings of an individual organism, but particularly the air, soil, and water. Although humans are considered a target species of particular interest, other species are of considerable importance as potential biologic targets. A ir pollution is a product of industrialization, technologic development, and increased urbanization. Humans may also be exposed to chemicals used in the agricultural environment as pesticides or in food processing that may persist as residues or ingredients in food products. Air contaminants are regulated in the United States by the Environmental Protection Agency (EPA) based on both health and esthetic considerations. Tables of regulated air contaminants and other regulatory issues that relate to air contaminants in the United States may be found at h ttp://www.epa.gov. Many states also have individual air contaminant regulations that may be more rigorous than those of the EPA. Many other nations and some supragovernmental organizations regulate air contaminants. T he United Nations Food and Agriculture Organization and the World Health Organization (FAO/WHO) Joint Expert Commission on Food Additives adopted the term acceptable daily intake (ADI) to denote the daily intake of a chemical from food that, during an entire lifetime, appears to be without appreciable risk. These guidelines are reevaluated as new information becomes available. In the United States, the Food and Drug Administration (FDA) and the Department of Agriculture are responsible for the regulation of contaminants such as pesticides, drugs, and chemicals in foods. Major international problems have occurred because of traffic among nations in contaminated or adulterated foods from countries whose regulations and enforcement of pure food and drug laws are lax or nonexistent.

**Ecotoxicology**

Ecotoxicology is concerned with the toxic effects of chemical and physical agents on populations and communities of living organisms within defined ecosystems; it includes the transfer pathways of those agents and their interactions with the environment. Traditional toxicology is concerned with toxic effects on individual organisms; ecotoxicology is concerned with the impact on populations of living organisms or on ecosystems.

 TOXICOLOGIC TERMS & DEFINITIONS Hazard & Risk H azard is the ability of a chemical agent to cause injury in a given situation or setting; the conditions of use and exposure are primary considerations. To assess hazard, one needs to have knowledge about both the inherent toxicity of the substance and the amounts to which individuals are liable to be exposed. Humans may be able to use potentially toxic substances when the necessary conditions minimizing absorption are established and respected. However, hazard is often a description based on subjective estimates rather than objective evaluation.

R isk is defined as the expected frequency of the occurrence of an undesirable effect arising from exposure to a chemical or physical agent. Estimation of risk makes use of dose-response data and extrapolation from the observed relationships to the expected responses at doses occurring in actual exposure situations. The quality and suitability of the biologic data used in such estimates are major limiting factors.

 **Routes of Exposure**

 The route of entry for chemicals into the body differs in different exposure situations. In the industrial setting, inhalation is the major route of entry. The transdermal route is also quite important, but oral ingestion is a relatively minor route. Consequently, primary prevention should be designed to reduce or eliminate absorption by inhalation or by topical contact. Atmospheric pollutants gain entry by inhalation and by dermal contact. Water and soil pollutants are absorbed through inhalation, ingestion, and dermal contact.

 **Duration of Exposure**

Toxic reactions may differ qualitatively depending on the duration of the exposure. A single exposure—or multiple exposures occurring over a brief period from seconds to 1 or 2 days—represents acute exposure. Multiple exposures continuing over a longer period of time represent chronic exposure. In the occupational setting, both acute (eg, accidental discharge) and chronic (eg, repetitive handling of a chemical) exposures occur. Exposures to chemicals found in the environment such as air and water pollutants often cause chronic exposure, but sudden large chemical releases may result in acute massive population exposure with serious or lethal consequences.

 ENVIRONMENTAL CONSIDERATIONS

 Certain chemical and physical characteristics are important for estimating the potential hazard involved for environmental toxicants. In addition to information regarding effects on different organisms, knowledge about the following properties is essential to predict the environmental impact: the degradability of the substance; its mobility through air, water, and soil; whether or not bioaccumulation occurs; and its transport and biomagnification through food chains. (See Box: Bioaccumulation & Biomagnification.) Chemicals that are poorly degraded (by abiotic or biotic pathways) exhibit environmental persistence and thus can accumulate. Typical examples of such chemicals include the persistent organic pollutants (POP) such as polychlorinated biphenyls and similar substances. Lipophilic substances such as the once-widespread organochlorine pesticides (eg, DDT) tend to bioaccumulate in body fat, resulting in tissue residues. Slowly released over time, these residues and their metabolites may have chronic adverse effects such as endocrine disruption. When the toxicant is incorporated into the food chain, biomagnification occurs as one species feeds on others and concentrates the chemical. Humans stand at the apex of the food chain. They may be exposed to highly concentrated pollutant loads as bioaccumulation and biomagnification occur. The pollutants that have the widest environmental impact are poorly degradable; are relatively mobile in air, water, and soil; exhibit bioaccumulation; and also exhibit biomagnification.

 **SPECIFIC CHEMICALS**

 **AIR POLLUTANTS**

 Five major substances account for about 98% of air pollution: carbon monoxide (CO, about 52%), sulfur oxides (about 14%), hydrocarbons (about 14%), nitrogen oxides (about 14%), and particulate matter (about 4%). The sources of these chemicals include transportation, industry, generation of electric power, space heating, and refuse disposal. Sulfur dioxide and smoke resulting from incomplete combustion of coal have been associated with acute adverse effects, particularly among the elderly and individuals with preexisting cardiac or respiratory disease. Ambient air pollution has been implicated as a contributing factor in bronchitis, obstructive ventilatory disease, pulmonary emphysema, bronchial asthma, and lung cancer. EPA standards for these substances apply to the general environment, and OSHA standards apply to workplace exposure.

 **Carbon Monoxide**

Carbon monoxide (CO) is a colorless, Carbon monoxide (CO) is a colorless, tasteless, odorless, and nonirritating gas, a byproduct of incomplete combustion. The average concentration of CO in the atmosphere is about 0.1 ppm; in heavy traffic, the concentration may exceed 100 ppm. The recommended 2008 threshold limit values (TLV-TWA and TLVSTEL) are shown in T able 56–1.

 **Mechanism of Action**

 CO combines reversibly with the oxygen-binding sites of hemoglobin and has an affinity for hemoglobin that is about 220 times that of oxygen. The product formed—carboxyhemoglobin— cannot transport oxygen. Furthermore, the presence of carboxyhemoglobin interferes with the dissociation of oxygen from the remaining oxyhemoglobin, thus reducing the transfer of oxygen to tissues. The brain and the heart are the organs most affected. Normal nonsmoking adults have carboxyhemoglobin levels of less than 1% saturation (1% of total hemoglobin is in the form of carboxyhemoglobin); this level has been attributed to the endogenous formation of CO from heme catabolism. Smokers may exhibit 5–10% saturation, depending on their smoking habits. A person breathing air containing 0.1% CO (1000 ppm) would have a carboxyhemoglobin level of about 50%.

 **B. Clinical Effects**

 The principal signs of CO intoxication are those of hypoxia and progress in the following sequence: (1) psychomotor impairment; (2) headache and tightness in the temporal area; (3) confusion and loss of visual acuity; (4) tachycardia, tachypnea, syncope, and coma; and (5) deep coma, convulsions, shock, and respiratory failure. There is great variability in individual responses to a given carboxyhemoglobin concentration. Carboxyhemoglobin levels below 15% may produce headache and malaise; at 25% many workers complain of headache, fatigue, decreased attention span, and loss of fine motor coordination. Collapse and syncope may appear at around 40%; with levels above 60%, death may ensue as a result of irreversible damage to the brain and myocardium. The clinical effects may be aggravated by heavy labor, high altitudes, and high ambient temperatures. Although CO intoxication is usually thought of as a form of acute toxicity, there is some evidence that chronic exposure to low levels may lead to undesirable effects, including the development of atherosclerotic coronary disease in cigarette smokers. The fetus may be quite susceptible to the effects of CO exposure.

**C. Treatment**

In cases of acute intoxication, removal of the individual from the exposure source and maintenance of respiration are essential, followed by administration of oxygen—the specific antagonist to CO—within the limits of oxygen toxicity. With room air at 1 atm, the elimination half-time of CO is about 320 minutes; with 100% oxygen, the half-time is about 80 minutes; and with hyperbaric oxygen (2–3 atm), the half-time can be reduced to about 20 minutes. If a hyperbaric oxygen chamber is readily available, it should be used in the treatment of CO poisoning for severely poisoned patients; however, there remain questions about its effectiveness. Progressive recovery from effectively treated CO poisoning, even of a severe degree, is often complete, although some patients demonstrate persistent impairment for a prolonged period of time.

 **Sulfur Dioxide**

 Sulfur dioxide (SO 2) is a colorless, irritant gas generated primarily by the combustion of sulfur-containing fossil fuels. The 2008 TLVs are given in T able 56–1.

1. **Mechanism of Action**

 On contact with moist membranes, SO 2 forms sulfurous acid, which is responsible for its severe irritant effects on the eyes, mucous membranes, and skin. Approximately 90% of inhaled SO 2 is absorbed in the upper respiratory tract, the site of its principal effect. The inhalation of SO 2 causes bronchial constriction; parasympathetic reflexes and altered smooth muscle tone appear to be involved. Exposure to 5 ppm SO 2 for 10 minutes leads to increased resistance to airflow in most humans. Exposures of 5–10 ppm are reported to cause severe bronchospasm; 10–20% of the healthy young adult population is estimated to be reactive to even lower concentrations. The phenomenon of adaptation to irritating concentrations has been reported in workers. However, current studies have not confirmed this phenomenon. Asthmatic individuals are especially sensitive to SO 2 .

1. **Clinical Effects and Treatment**

The signs and symptoms of intoxication include irritation of the eyes, nose, and throat and reflex bronchoconstriction. In asthmatic subjects, exposure to SO 2 may result in an acute asthmatic episode. If severe exposure has occurred, delayed-onset pulmonary edema may be observed. Cumulative effects from chronic lowlevel exposure to SO 2 are not striking, particularly in humans but these effects have been associated with aggravation of chronic cardiopulmonary disease. When combined exposure to high respirable particulate loads and SO 2 occurs, the mixed irritant load may increase the toxic respiratory response. Treatment is not specific for SO 2 but depends on therapeutic maneuvers used in the treatment of irritation of the respiratory tract and asthma.

 **Nitrogen Oxides**

Nitrogen dioxide (NO 2 ) is a brownish irritant gas sometimes associated with fires. It is formed also from fresh silage; exposure of farmers to NO 2 in the confines of a silo can lead to silo-filler’s disease. The 2008 TLVs are shown in T able

**Mechanism of Action**

 NO 2 is a relatively insoluble deep lung irritant capable of producing pulmonary edema. The type I cells of the alveoli appear to be the cells chiefly affected on acute exposure. At higher exposure, both type I and type II alveolar cells are damaged. Exposure to 25 ppm of NO 2 is irritating to some individuals; 50 ppm is moderately irritating to the eyes and nose. Exposure for 1 hour to 50 ppm can cause pulmonary edema and perhaps subacute or chronic pulmonary lesions; 100 ppm can cause pulmonary edema and death.

1. **Clinical Effects and Treatment**

 The signs and symptoms of acute exposure to NO 2 include irritation of the eyes and nose, cough, mucoid or frothy sputum production, dyspnea, and chest pain. Pulmonary edema may appear within 1–2 hours. In some individuals, the clinical signs may subside in about 2 weeks; the patient may then pass into a second stage of abruptly increasing severity, including recurring pulmonary edema and fibrotic destruction of terminal bronchioles (bronchiolitis obliterans). Chronic exposure of laboratory animals to 10–25 ppm NO 2 has resulted in emphysematous changes; thus, chronic effects in humans are of concern. There is no specific treatment for acute intoxication by NO 2 ; therapeutic measures for the management of deep lung irritation and noncardiogenic pulmonary edema are used. These measures include maintenance of gas exchange with adequate oxygenation and alveolar ventilation. Drug therapy may include bronchodilators, sedatives, and antibiotics.

Some metals such as iron are essential for life, whereas others such as lead are present in all organisms but serve no useful biologic purpose. Some of the oldest diseases of humans can be traced to heavy metal poisoning associated with metal mining, refining, and use. Even with the present recognition of the hazards of heavy metals, the incidence of intoxication remains significant, and the need for preventive strategies and effective therapy remains high. Toxic heavy metals interfere with the function of essential cations, cause enzyme inhibition, generate oxidative stress, and alter gene expression. As a result, multisystem signs and symptoms are a hallmark of heavy metal intoxication. When intoxication occurs, chelator molecules (from chela “claw”), or their in vivo biotransformation products, may be used to bind the metal and facilitate its excretion from the body. Chelator drugs are discussed in the second part of this chapter.

■ **TOXICOLOGY OF HEAVY METALS**

 **LEAD**

 Lead poisoning is one of the oldest occupational and environmental diseases in the world. Despite its recognized hazards, lead continues to have widespread commercial application, including production of storage batteries (nearly 90% of US consumption), ammunition, metal alloys, solder, glass, plastics, pigments, and ceramics. Corrosion of lead plumbing in older buildings or supply lines may increase the lead concentration of tap water. Environmental lead exposure, ubiquitous by virtue of the anthropogenic distribution of lead to air, water, and food, has declined considerably in the last three decades as a result of the elimination of lead as an additive in gasoline, as well as diminished contact with lead based paint and other lead-containing consumer products, such as lead solder in canned food. Although these public health measures, together with improved workplace conditions, have decreased the incidence of serious overt lead poisoning, there remains considerable concern over the effects of low-level lead exposure. Extensive evidence indicates that lead may have subtle subclinical adverse effects on neurocognitive function and on blood pressure at low blood lead concentrations formerly not recognized as harmful. Lead serves no useful purpose in the human body. In key target organs such as the developing central nervous system, no level of lead exposure has been shown to be without deleterious effects.

 **Pharmacokinetics**

 Inorganic lead is slowly but consistently absorbed via the respiratory and gastrointestinal tracts. Inorganic lead is poorly absorbed through the skin. Absorption of lead dust via the respiratory tract is the most common cause of industrial poisoning. The intestinal tract is the primary route of entry in nonindustrial exposure ( Table 57–1 ). Absorption via the gastrointestinal tract varies with the nature of the lead compound, but in general, adults absorb about 10–15% of the ingested amount, whereas young children absorb up to 50%. Low dietary calcium, iron deficiency, and ingestion on an empty stomach all have been associated with increased lead absorption.

Once absorbed from the respiratory or gastrointestinal tract, lead enters the bloodstream, where approximately 99% is bound to erythrocytes and 1% is present in the plasma. Lead is subsequently distributed to soft tissues such as the bone marrow, brain, kidney, liver, muscle, and gonads; then to the subperiosteal surface of bone; and later to bone matrix. Lead also crosses the placenta and poses a potential hazard to the fetus. The kinetics of lead clearance from the body follows a multicompartment model, composed predominantly of the blood and soft tissues, with a half-life of 1–2 months; and the skeleton, with a half-life of years to decades. Approximately 70% of the lead that is eliminated appears in the urine, with lesser amounts excreted through the bile, skin, hair, nails, sweat, and breast milk. The fraction not undergoing prompt excretion, approximately half of the absorbed lead, may be incorporated into the skeleton, the repository of more than 90% of the body lead burden in most adults. In patients with high bone lead burdens, slow release from the skeleton may elevate blood lead concentrations for years after exposure ceases, and pathologic high bone turnover states such as hyperthyroidism or prolonged immobilization may result in frank lead intoxication. Migration of retained lead bullet fragments into

a joint space or adjacent to bone has been associated with the development of lead poisoning signs and symptoms years or decades after an initial gunshot injury.

 **Pharmacodynamics**

 Lead exerts multisystemic toxic effects that are mediated by multiple modes of action, including inhibition of enzymatic function; interference with the action of essential cations, particularly calcium, iron, and zinc; generation of oxidative stress; changes in gene expression; alterations in cell signaling; and disruption of the integrity of membranes in cells and organelles.

1. **Nervous System**

The developing central nervous system of the fetus and young child is the most sensitive target organ for lead’s toxic effect. Epidemiologic studies suggest that blood lead concentrations even less than 5 mcg/dL may result in subclinical deficits in neurocognitive function in lead-exposed young children, with no demonstrable threshold for a “no effect” level. The dose response between low blood lead concentrations and cognitive function in young children is nonlinear, such that the decrement in intelligence associated with an increase in blood lead from less than 1 to 10 mcg/dL (6.2 IQ points) exceeds that associated with a change from 10 to 30 mcg/dL (3.0 IQ points). A dults are less sensitive to the central nervous system effects of lead, but long-term exposure to blood lead concentrations in the range of 10–30 mcg/dL may be associated with subtle, subclinical effects on neurocognitive function. At blood lead concentrations higher than 30 mcg/dL, behavioral and neurocognitive signs or symptoms may gradually emerge, including irritability, fatigue, decreased libido, anorexia, sleep disturbance, impaired visualmotor coordination, and slowed reaction time. Headache, arthralgias, and myalgias are also common complaints. Tremor occurs but is less common. Lead encephalopathy, usually occurring at blood lead concentrations higher than 100 mcg/dL, is typically accompanied by increased intracranial pressure and may cause ataxia, stupor, coma, convulsions, and death. Recent epidemiological studies suggest that lead may accentuate an age-related decline in cognitive function in older adults. In experimental animals, developmental lead exposure has been associated with increased expression of beta-amyloid, oxidative DNA damage, and Alzheimer’s-type pathology in the aging brain. There is wide interindividual variation in the magnitude of lead exposure required to cause overt lead-related signs and symptoms. Overt peripheral neuropathy may appear after chronic highdose lead exposure, usually following months to years of blood lead concentrations higher than 100 mcg/dL. Predominantly motor in character, the neuropathy may present clinically with painless weakness of the extensors, particularly in the upper extremity, resulting in classic wrist-drop. Preclinical signs of leadinduced peripheral nerve dysfunction may be detectable by electrodiagnostic testing.

 B. Blood L ead can induce an anemia that may be either normocytic or microcytic and hypochromic. Lead interferes with heme synthesis by blocking the incorporation of iron into protoporphyrin IX and by inhibiting the function of enzymes in the heme synthesis pathway, including aminolevulinic acid dehydratase and ferrochelatase. Within 2–8 weeks after an elevation in blood lead concentration (generally to 30–50 mcg/dL or greater), increases in heme precursors, notably free erythrocyte protoporphyrin or its zinc chelate, zinc protoporphyrin, may be detectable in whole blood. Lead also contributes to anemia by increasing erythrocyte membrane fragility and decreasing red cell survival time. Frank hemolysis may occur with high exposure. Basophilic stippling on the peripheral blood smear, thought to be a consequence of lead inhibition of the enzyme 3’,5’-pyrimidine nucleotidase, is sometimes a suggestive— albeit insensitive and nonspecific—diagnostic clue to the presence of lead intoxication.

 C**. Kidneys**

Chronic high-dose lead exposure, usually associated with months to years of blood lead concentrations greater than 80 mcg/dL, may

result in renal interstitial fibrosis and nephrosclerosis. Lead nephropathy may have a latency period of years. Lead may alter uric acid excretion by the kidney, resulting in recurrent bouts of gouty arthritis (“saturnine gout”). Acute high-dose lead exposure sometimes produces transient azotemia, possibly as a consequence of intrarenal vasoconstriction. Studies conducted in general population samples have documented an association between blood lead concentration and measures of renal function, including serum creatinine and creatinine clearance. The presence of other risk factors for renal insufficiency, including hypertension and diabetes, may increase susceptibility to lead-induced renal dysfunction.

 **D. Reproductive Organs**

High-dose lead exposure is a recognized risk factor for stillbirth or spontaneous abortion. Epidemiologic studies of the impact of low-level lead exposure on reproductive outcome such as low birth weight, preterm delivery, or spontaneous abortion have yielded mixed results. However, a well-designed nested case-control study detected an odds ratio for spontaneous abortion of 1.8 (95% CI 1.1–3.1) for every 5 mcg/dL increase in maternal blood lead across an approximate range of 5–20 mcg/dL. Recent studies have linked prenatal exposure to low levels of lead (eg, maternal blood lead concentrations of 5–15 mcg/dL) to decrements in physical and cognitive development assessed during the neonatal period and early childhood. In males, blood lead concentrations higher than 40 mcg/dL have been associated with diminished or aberrant sperm production.

1. **Gastrointestinal Tract**

Moderate lead poisoning may cause loss of appetite, constipation, and, less commonly, diarrhea. At high dosage, intermittent bouts of severe colicky abdominal pain (“lead colic”) may occur. The mechanism of lead colic is unclear but is believed to involve spasmodic contraction of the smooth muscles of the intestinal wall, mediated by alteration in synaptic transmission at the smooth muscle-neuromuscular junction. In heavily exposed individuals with poor dental hygiene, the reaction of circulating lead with sulfur ions released by microbial action may produce dark deposits of lead sulfide at the gingival margin (“gingival lead lines”). Although frequently mentioned as a diagnostic clue in the past, in recent times this has been a relatively rare sign of lead exposure.

 **F. Cardiovascular System**

Epidemiologic, experimental, and in vitro mechanistic data indicate that lead exposure elevates blood pressure in susceptible individuals. In populations with environmental or occupational lead exposure, blood lead concentration is linked with increases in systolic and diastolic blood pressure. Studies of middle-aged and elderly men and women have identified relatively low levels of lead exposure sustained by the general population to be an independent risk factor for hypertension. In addition, epidemiologic studies suggest that low to moderate levels of lead exposure are risk factors for increased cardiovascular mortality. Lead can also elevate blood pressure in experimental animals.

**Treatment**

 A. Inorganic Lead Poisoning Treatment of inorganic lead poisoning involves immediate termination of exposure, supportive care, and the judicious use of chelation therapy. (Chelation is discussed later in this chapter.) Lead encephalopathy is a medical emergency that requires intensive supportive care. Cerebral edema may improve with corticosteroids and mannitol, and anticonvulsants may be required to treat seizures. Radiopacities on abdominal radiographs may suggest the presence of retained lead objects requiring gastrointestinal decontamination. Adequate urine flow should be maintained, but overhydration should be avoided. Intravenous edetate calcium disodium (CaNa 2 EDTA) is administered at a dosage of 1000– 1500 mg/m 2 /d (approximately 30–50 mg/kg/d) by continuous infusion for up to 5 days. Some clinicians advocate that chelation treatment for lead encephalopathy be initiated with an intramuscular injection of dimercaprol, followed in 4 hours by concurrent administration of dimercaprol and EDTA. Parenteral chelation is limited to 5 or fewer days, at which time oral treatment with another chelator, succimer, may be instituted. In symptomatic lead intoxication without encephalopathy, treatment may sometimes be initiated with succimer. The end point for chelation is usually resolution of symptoms or return of the blood lead concentration to the premorbid range. In patients with chronic exposure, cessation of chelation may be followed by an upward rebound in blood lead concentration as the lead re-equilibrates from bone lead stores. Although most clinicians support chelation for symptomatic patients with elevated blood lead concentrations, the decision to chelate asymptomatic subjects is more controversial. Since 1991, the Centers for Disease Control and Prevention (CDC) has recommended chelation for all children with blood lead concentrations of 45 mcg/dL or greater. However, a recent randomized, double-blind, placebo-controlled clinical trial of succimer in children with blood lead concentrations between 25 mcg/dL and 44 mcg/dL found no benefit on neurocognitive function or longterm blood lead reduction. Prophylactic use of chelating agents in the workplace should never be a substitute for reduction or prevention of excessive exposure. Management of elevated blood lead levels in children and adults should include a conscientious effort to identify and reduce all potential sources of future lead exposure. Many local, state, or national governmental agencies maintain lead poisoning prevention programs that can assist in case management. Blood lead screening of family members or coworkers of a lead poisoning patient is often indicated to assess the scope of the exposure. Although the CDC blood lead level of concern for childhood lead poisoning of 10 mcg/dL has not been revised since 1991, the adverse impact of lower levels on children is widely acknowledged, and primary prevention of lead exposure is receiving increased emphasis. Although the US Occupational Safety and Health Administration (OSHA) lead regulations introduced in the late 1970s mandate that workers be removed from lead exposure for blood lead levels higher than 50–60 mcg/dL, an expert panel in 2007 recommended that removal be initiated for a single blood lead level greater than 30 mcg/dL, or when two successive blood lead levels measured over a 4-week interval are 20 mcg/dL or more. The longer-term goal should be for workers to maintain blood lead levels at lower than 10 mcg/dL, and for pregnant women to avoid occupational or avocational exposure that would result in blood lead levels higher than 5 mcg/dL. Environmental Protection Agency (EPA) regulations effective since 2010 require that contractors who perform renovation, repair, and painting projects that disturb lead-based paint in pre-1978 residences and child-occupied facilities must be certified and must follow specific work practices to prevent lead contamination.