9.07
The Medical Geochemistry of Dusts, Soils, and Other Earth Materials

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9.07.1 INTRODUCTION

"Town clenched in suffocating grip of asbestos"
USA Today, article on Libby, Montana, February, 2000

"Researchers find volcanoes are bad for your health… long after they finish erupting"
University of Warwick Press Release, 1999

"Toxic soils plague city—arsenic, lead in 5 neighborhoods could imperil 17,000 residents"
Denver Post, 2002

"Ill winds—dust storms ferry toxic agents between countries and even continents"
Science News, 2002

A quick scan of newspapers, television, science magazines, or the internet on any given day has a fairly high likelihood of encountering a story (usually accompanied by a creative headline such as those above) regarding human health concerns linked to dusts, soils, or other earth materials. Many such concerns have been recognized and studied for decades, but new concerns arise regularly.

Earth scientists have played significant roles in helping the medical community understand some important links between earth materials and human health, such as the role of asbestos mineralogy in disease (Skinner *et al.*, 1988; Ross, 1999; Holland and Smith, 2001), and the role of dusts generated by the 1994 Northridge, California, earthquake in an outbreak of Valley Fever (Jibson *et al.*, 1998; Schneider *et al.*, 1997).

Earth science activities tied to health issues are growing (Skinner and Berger, 2003), and are commonly classified under the emerging discipline of *medical geology* (Finkelman *et al.*, 2001; Selinus and Frank, 2000; Selinus, in press).

Medical geochemistry (also referred to as environmental geochemistry and health: Smith and Huyck (1999), Appleton *et al.* (1996)) can be considered as a diverse subdiscipline of medical geology that deals with human and animal health in the context of the Earth's geochemical cycle (Figure 1). Many medical geochemistry studies have focused on how chemical elements in rocks, soils, and sediments are transmitted via water or vegetation into the food chain, and how regional geochemical variations can result in disease clusters either through dietary deficiency of essential elements or dietary excess of toxic elements.

This chapter focuses on a somewhat narrower area of medical geochemistry: the study of mechanisms of uptake of earth materials by humans and animals and their reactions to these materials. In order for earth materials to affect health, they must first interact with the body across key interfaces such as the respiratory tract, gastrointestinal tract, skin, and eyes. In some way, all of these interfaces require the earth materials to interact chemically with water-based body fluids such as lung fluids, gastrointestinal fluids, saliva, or blood plasma.

The primary goal of this chapter, co-authored by a geochemist and a toxicologist, is to provide both geochemists and scientists from health disciplines with an overview of the potential geochemical mechanisms by which earth materials can influence human health. It is clear that significant opportunities for advancement in this arena will require continued and increased research collaborations between geochemists and their counterparts in the health disciplines.

9.07.2 EARTH MATERIALS LINKED TO HUMAN HEALTH

A wide variety of natural and anthropogenic materials and chemicals are recognized to influence human health. In this chapter, we consider earth materials to include a fairly broad range of solids and gases that: are produced by natural earth processes; are liberated from the earth as a result of human activities; or that are produced from the earth by humans and transformed for use in society. Examples of earth materials that have been the focus of health concerns (Tables 1 and 2) include:

- Mineral dusts of asbestos and some other asbestiform or fibrous minerals, silica, and coal. These include dusts generated by the natural weathering of rocks, and dusts generated

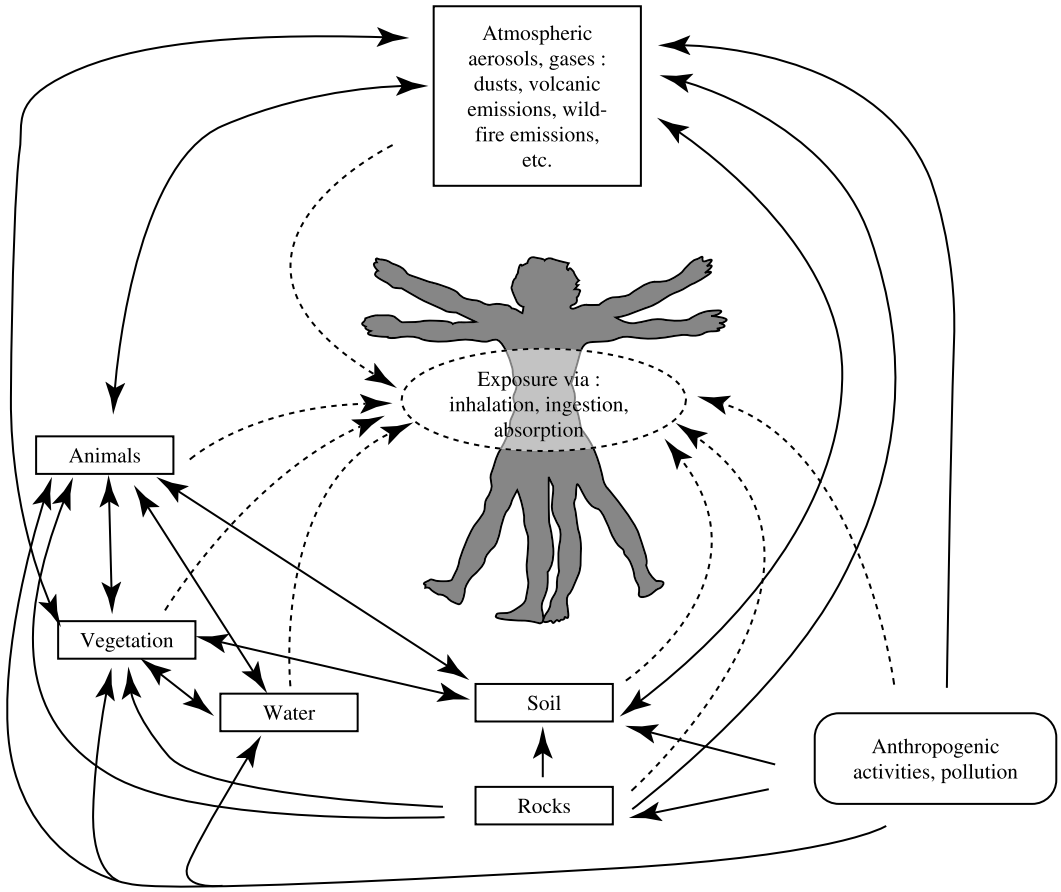

Figure 1 Potential human exposure routes within the earth's geochemical cycle can come from a wide variety of both natural and anthropogenic sources.

by anthropogenic activities such as mining, industrial processes, and construction.
- Volcanic ash and gases.
- Soils and dusts containing heavy metals, organic contaminants, or pathogens.
- Solid, gaseous, and aqueous wastes or by-products of mining, mineral processing, smelting, and energy production.
- Construction materials such as cement, concrete, aggregate, mineral and glass fiber insulation, and gypsum wallboard.
- Dusts released by building collapse or demolition.

A wide variety of elements found in earth materials can be associated with specific health problems (WHO, 1996; Taylor and Williams, 1998; Goyer and Clarkson, 2001). Essential/beneficial elements (Table 2) are those that are required for the proper physiologic function of the body, and so their associated health problems may result from either deficiencies or excesses. A variety of elements, primarily metals or metalloids, have no known natural physiological benefits but are considered toxic in excess exposure.

Environmental and health effects of radionuclides are summarized by Siegel and Bryan, (see Chapter 9.06). Potential environmental effects of hydrocarbons and organic chemicals are addressed in other chapters, and will not be discussed here. Environmental and health effects of arsenic, selenium, and mercury are addressed in greater detail elsewhere in this volume, including Chapters 9.02 and 9.04. Further information on the environmental geochemistry of metals is presented by Callender (see Chapter 9.03).

9.07.3 OVERVIEW OF THE HEALTH EFFECTS OF EARTH MATERIALS

There are a variety of diseases or health problems that have been tied to exposure to the earth materials discussed previously, or that result from industrial exposure to a wide variety of chemicals or materials. Because these are far too numerous to list in detail, the interested reader is referred to toxicological reviews such as those by Sullivan and Krieger (2001) and Klassen (2001). Examples of illnesses that are known, suspected or

Table 1 Examples of earth materials and their sources with known or postulated health effects.

Material	*Examples of potential sources*	*Primary exposure pathways,* health effects
Asbestos	Dusts from: industrial, commercial products (insulation, brake linings, building products, others) and activities; asbestos accessory minerals in other industrial/commercial products (some vermiculite, talc, other products); natural sources (via natural weathering, erosion of asbestos-bearing rocks) may provide low-level exposures.	*Inhalation*. Asbestosis; lung cancer; pleural effusion, thickening, plaques; mesothelioma cancer. Associated secondary illnesses include heart failure, lung infection. *Ingestion*. Has been proposed as a trigger of GI cancers, other health effects; however, links have not been demonstrated with certainty.
Crystalline silica	Dusts generated by mining, other industrial activities. Dusts produced by erosion of friable, silica-rich rocks (i.e., some ash flow tuffs, diatomaceous earth deposits).	*Inhalation*. Silicosis, industrial bronchitis with airflow limitation, progressive massive fibrosis. Associated illnesses include opportunistic infections, silica nethropathy, lung cancer.
Coal dust, coal fly ash	Dusts generated by coal mining, processing, and combustion activities.	*Inhalation*. "Black lung"— includes CWP, progressive massive fibrosis, chronic airway obstruction or bronchitis, emphysema; possible silicosis due to intermixed crystalline silica.
Other mineral dusts	Dusts of talc, kaolinite, other clays, micas, aluminosilicates. Sources include dusts generated from industrial, commercial activities and products.	*Inhalation*. Mineral-specific fibrosis, such as talcosis; also silicosis and asbestosis due to intermixed crystalline silica and asbestos.
Man-made mineral fibers	Glass wool (fiberglass); mineral wool (slag, rock wool).	*Inhalation*. Irritation of upper respiratory tract, skin. No ties to lung cancers, lung fibrosis.
Cement/concrete dust	Dusts from cement, concrete manufacturing. Concrete dusts generated by demolition, construction activities.	*Inhalation, contact with exposed mucous membranes or moist skin*. Irritation of eyes, throat, respiratory tract; ulceration of mucous surfaces. Effects largely tied to alkalinity of the dusts.
Volcanic ash	Atmospheric particulates generated by eruptions. Natural and anthropogenic disturbance of volcanic ash deposits, such as earthquakes, landslides, construction activities.	*Inhalation*. Irritation of respiratory tract; asthma; potential effects of crystalline silica and iron-rich particles within ash.
Volcanic gases, vog, laze	Sulfur dioxide, hydrogen fluoride, hydrogen chloride, other acid gases emanating from active volcanoes. Acidic aerosol droplets formed when hot lava contacts seawater and causes it to boil.	*Inhalation, contact with exposed mucous membranes or moist skin*. Irritation of eyes, throat, respiratory tract; ulceration of mucous surfaces. Effects largely tied to acidity of the gases and droplets. If gases are in sufficiently high concentration, toxic effects can also result.
Pathogens	Soils, and dusts generated from soils, that host pathogens such as bacteria and fungi.	*Inhalation, ingestion*. Asthma and pathogen-specific diseases such as Valley Fever (from the soil fungus *C. Immitis*) and anthrax (*B. anthracis*). *Percutaneous absorption*. Pathogen-related infections can develop through breaks in the skin.

References include: Holland and Smith (2001), Mossman and Gee (1989), Skinner *et al.* (1988), Selikoff and Lee (1978), SSDC (1988), Daroowalla (2001), Castranova and Vallyathan (2000), Castranova (2000), Daroowalla (2001), Hesterberg *et al.* (2001), CDC (1986), Baxter *et al.* (1999,1983), Wilson *et al.* (2000), Sutton *et al.* (1997), Bultman *et al.* (in press), and Griffin *et al.* (2002).

Table 2 Examples of heavy metals or metalloids, their potential sources (with an emphasis on earth materials), and health effects associated with their major exposure pathways.

Chemical element	*Examples of possible earth material sources enriched or depleted in element*	*Health effects associated with deficiency*	*Health effects associated with excess for the dominant exposure route(s)*
Essential/beneficial element			
Calcium (Ca)	Rocks and soils enriched in bioavailable calcium carbonate (limestone, caliche, etc.). Hard waters, waters affected by acid-rock drainage. Cement, concrete, fly ash, many other industrial/ commercial materials or by-products.	Bone deformities (rickets); tetany (spasms of extremities).	*Ingestion*. Atherosclosis, cataracts, gall stones.
Cobalt (Co)	Some types of nickel or silver ore deposits. Soils and waters affected by smelter emissions, mining wastes and by-products. Some rocks such as black shales, ultramafic rocks.	Anemia, anorexia.	*Ingestion*. Cardiomyopathy, hypothyroidism, polycythemia (excess of red blood cells), cancer. *Inhalation.* Respiratory irritation. "Hard metal" pneumoconiosis. *Percutaneous*. Allergic dermatitis.
Copper (Cu)	Cu-rich ore deposits (i.e., porphyry, massive sulfide, sediment-hosted). Soils and waters affected by smelter emissions, mining wastes and byproducts. Cu locally enriched in some rocks (continental redbed sediments, basalts).	Anemia, Menke's syndrome.	*Ingestion, Inhalation*. Wilson's disease (associated with Cu buildup in organs), intestinal and liver inflammation, hemolysis (destruction of red blood cells, with diffusion of hemoglobin into surrounding fluids), hyperglycemia.
Chromium (Cr)	Commonly enriched in ultramafic rocks and their associated ore deposits. Much naturally occurring Cr is relatively insoluble chromite. Soluble Cr may occur naturally in evaporative lake sediments or other evaporative environments, as a trace element within other soluble salts. Anthropogenic Cr can occur in soils, sediments, and waters affected by industrial wastes and byproducts (i.e., leather tanning, electroplating., cement use).	Cr(III) is essential— deficiencies result in defective glucose metabolism, hyperlipidemia, corneal opacity	*Inhalation, ingestion, percutaneous absorption*. Irritation of and generation of lesions in skin, respiratory tract, and gastric and intestinal mucosa; contact dermatitis; pulmonary edema. Acute kidney failure. Long-term risk for lung cancers. Pneumoconiosis from exposure to chromite ore dust.

(continued)

Table 2 (continued).

Chemical element	*Examples of possible earth material sources enriched or depleted in element*	*Health effects associated with deficiency*	*Health effects associated with excess for the dominant exposure route(s)*
Fluorine (F)	Commonly associated with limestones, fluorine-rich granites and associated ore deposits. May be present in coal combustion byproducts, fly ash.	Dental decay, possible growth retardation.	*Ingestion* > *inhalation*. At low levels: mottling of tooth enamel. At high levels: fluorosis—includes wide variety of health problems such as hyperparathyroidism, calcification of soft tissues, interference with collagen formation, severe skeletal deformity.
Iodine (I)	Brines. Some evaporite rocks, and sediments formed in evaporative environments.	Fetal problems, including abortion, stillbirths, congenital anomalies, neurological cretinism. Goiter, hypothyroidism, impaired mental function, increased susceptibility to radiation.	*Ingestion*. Hyperthyroidism
Iron (Fe)	Common rock-forming element. Enriched in many rocks, ores, soils, mine wastes, smelter emissions, etc. Pyrite (an iron sulfide) is a source of readily available iron and occurs in many different rocks and ores.	Anemias.	*Ingestion*. Most toxicity results from accidental ingestion of iron-containing medicines. Hemachromatosis, siderosis, cardiac failure, cancer.
Lithium (Li)	Salts from evaporative brines, evaporative lake sediments.	Manic depression.	*Ingestion*. Most toxicity results from excess medicinal use. Adverse neuromuscular, central nervous system, cardiovascular, gastrointestinal, and renal effects.
Magnesium (Mg)	Dolomite rock; cement and concrete; evaporative brines.	Convulsions.	*Ingestion*. Primarily from chronic use of Mg-containing drugs by people with renal dysfunction. Anesthesia, hypotension, electroardiograph abnormalities, secondary central nervous system effects. *Inhalation*. Mg-oxide can cause metal fume fever.
Molybdenum (Mo)	Mo-rich ore deposits (i.e., porphyry deposits); black shales.	Growth depression, keratinization effects, hyperurinemia.	*Ingestion*. High uric acid in serum and urine, loss of appetite, diarrhea, slow growth, anemia, “gout-like” lesions. Molybdenosis.

Manganese (Mn)	Present in limestones and other rocks formed as chemical precipitates. Common in many types of ore deposits.	Skeletal deformities, testicular dysfunction.	*Inhalation* > *ingestion* *Inhalation*. Mn-pneumonitis from acute exposure. Chronic exposure leads to manganism, other neurological and phychological disorders. *Ingestion*. Liver cirrhosis.
Selenium (Se)	Black shales, phosphatic sediments. Sometimes enriched in soluble evaporative salts formed in evaporative lake sediments, and in agricultural soils developed from Se-rich rocks. Smelter particulates and smelter-affected soils. *Some rock and sediment types, as well as their derived soils, are naturally depleted in Se, for example some dust-derived sediments (loess), some granites or gneissic metamorphic rocks.*	Liver necrosis, endemic cardio-myopathy (Kesham disease), osteoarthropathy (Kashin's Beck disease), membrane malfunction.	*Ingestion*. Teratogenesis (triggers birth defects), fetal toxicity, liver and kidney damage, cancer, brittle hair and nails, skin lesions, some effects on central, peripheral nervous systems. Selenosis.
Zinc (Zn)	Zn-rich ore deposits (i.e., massive sulfide, sediment-hosted). Soils and waters affected by smelter emissions, mining wastes and by-products. Enriched in some rocks, such as black shales, basalts.	Anorexia, dwarfism, anemia, hypogonadism, hyperkeratosis, acrodermatitis, enteropathica, depressed immune response, teratogenic effects.	*Ingestion*. Hyperchronic anemia. *Inhalation*. Metal fume fever at high doses.
Nonessential metals, toxic in excess			
Aluminum (Al)	Common rock-forming mineral, although most Al-bearing silicates quite insoluble. Potentially soluble Al-hydroxides, hydroxysulfates form in lateric ore deposits, tropical soils, and precipitate in streams affected by acid-rock drainage. Al-rich soluble salts can occur in evaporative lake sediments, and in mine wastes. Potentially reactive forms in cement, concrete, smelter emissions, coal fly ash.	None recognized.	*Ingestion* > *inhalation*. Osteomalacia (softening of bones). Neurotoxicity effects include: neurofibrillary tangles; behavioral changes; possible causative agent of Alzheimer's disease, some human dementia syndromes. Exposure to Al dusts can trigger lung fibrosis.

(continued)

Table 2 (continued).

Chemical element	*Examples of possible earth material sources enriched or depleted in element*	*Health effects associated with deficiency*	*Health effects associated with excess for the dominant exposure route(s)*
Arsenic (As)	Soils and waters affected by emissions from smelters, power plants. Soils and waters affected by mining wastes and by-products. Some playa lake sediments. Soils and dusts derived from naturally As-enriched rocks and sediments. Waters that have leached As from As-rich rocks, soils, and sediments. Pesticides, other industrial chemicals. By-products or wastes from chemical manufacturing or other industrial processes.	None recognized.	*Ingestion, inhalation*. Acute poisoning can lead to a wide variety of maladies, including: systemic hypotension; GI pain and bleeding; pulmonary edema; anemia, destruction of red blood cells; liver necrosis, kidney failure; encephalopathy and other central and peripheral nervous system disorders. Chronic toxicity can lead to: systemic hypotension; skin disorders such as eczema, hyperkeratosis, melanosis, ulceration, skin cancers; blood problems such as anemia, acute leukemia; kidney failure; delirium, encephalopathy, seizures, neuropathy.
Beryllium (Be)	Enriched in relatively insoluble form in silicates in pegmatites; also enriched in some coals and alkalic rocks and their associated mineral deposits. Soils and waters affected by emissions from coal-fired power plants.	None recognized.	*Inhalation*. Exposures primarily industrial. Chemical pneumonitis, berylliosis, cancer. *Percutaneous*. Contact dermatitis, formation of granulatomous lesions; lesions from exposure to soluble forms.
Cadmium (Cd)	Enriched in many zinc ores, black shales, phosphatic shales. Can be enriched in soils, sediments, and waters affected by: emissions from smelters, power plants; agricultural applications of sewage sludge; mining and industrial wastes and by-products; industrial wastes, by-products, and trash (i.e., battery production, leather tanning, electroplating, cement use).	None recognized.	*Inhalation, ingestion*. Acute exposure leads to: GI tract distress, gastroenteritis, liver and kidney damage, cardiomyopathy, metabolic acidosis, irritation of nasopharyngeal tract, pneumonitis. Chronic exposure can lead to: obstructive lung disease, bronchitis, emphysema, lung cancer, kidney damage, secondary skeletal system effects (osteoporosis, osteomalacia—brittleness and softening of bones; Itai-itai disease).

Lead (Pb)	Soils and waters affected by leaded gas, smelter emissions, mining wastes and by-products. Dusts, soils, and debris containing lead-bearing paint. Foods grown in lead-rich soils. Soils and dusts derived from naturally lead-enriched rocks. Waters that have leached lead from supply pipes.	None recognized.	*Inhalation, ingestion*. Acute poisoning leads to acute encphalopathy, renal failure and severe GI distress. Chronic poisoning leads to central nervous system problems, impaired neurobehavioral function, diminished gross and fine motor development in children, kidney disease, hypertension, anemia, and other hematologic effects.
Mercury (Hg)	Soils and waters affected by atmospheric deposition of Hg from volcanoes, smelters, power plants. Soils and waters affected by mining and industrial wastes and by-products. Environmental contributions from pesticides, paints, antiseptic agents, thermometers, vacuum pumps, and a wide variety of other commercial, industrial, and pharmaceutical chemicals and products.	None recognized.	*Inhalation, ingestion, percutaneous absorption*. Chronic exposure leads to: tremors and other central nervous system disorders; kidney damage, some pulmonary damage. Acute exposure produces: severe damage to the central nervous system peripheral nervous system, and GI system; kidney failure. Mercury is also a potent teratogen.
Nickel (Ni)	Enriched in ultramafic rocks and their associated mineral deposits; also enriched in many black shales, some phophatic shales. Soils, sediments, and waters affected by mining wastes, smelter emissions, power plants, industrial wastes and by-products.	None recognized.	*Inhalation*. Chronic bronchitis, emphysema, reduced lung capacity, and cancers of the lungs and nasal sinus. *Ingestion*. death (due to cardiac arrest), gastrointestinal effects (nausea, cramps, diarrhea, vomiting), effects on blood, liver, kidneys. Also neurological effects (giddiness, weariness).
Radionuclides (including uranium, radium, radon, thorium, plutonium)	A variety of rocks, soils, sediments, dusts, Tores, and other solids are enriched in uranium (U) and thorium, which can decay to radon, radium, and other daughter products. Ground waters that have traveled through U-rich rocks, soils, and sediments.	None recognized.	*Ingestion*. Common exposure route for uranium, which can triggeracute renal damage and failure. *Inhalation*. Primarily is exposure route for fine radionuclide particulates, radon gas, which can decay to other radioactive daughter products and lead to lung cancer.

This table is modeled after one in Taylor and Williams (1998) with additional information from Goyer and Clarkson (2001), ATSDR (1990; 1994; 1997; 1999a–d; 2000a,b), Geller (2001), WHO (1996), Gibly and Sullivan (2001), Derbyshire (in press), Fisher (2001), Yip *et al.* (2001), Waalkes *et al.* (2001), Cook *et al.* (1993), and Landrigan (1990). Information on element enrichments in earth materials is from Smith and Huyck (1999) and Plumlee (1999). For a discussion of elements not included in this table (e.g., thallium, antimony, bismuth, silver, tin, gallium, etc.) the reader is referred to summaries in Goyer and Clarkson (2001) and Sullivan and Krieger (2001).

postulated to result from excessive acute or chronic exposures to toxins that can be contained in earth materials, include (Tables 1 and 2):

- cancers of the lungs, skin, kidneys, mesothelium, bladder, and other organs;
- pneumoconioces such as asbestosis, silicosis, black lung disease, and other diseases tied to long-term exposure to mineral dusts. These may also trigger secondary diseases such as congestive heart failure;
- pathogen-triggered diseases where the pathogen is associated with dusts or soils (valley fever, naturally occurring anthrax);
- chronic lung illnesses, such as asthma and emphysema;
- chemical injury to, irritation of, or allergic reaction in the skin, eyes, throat, respiratory tract, and digestive tract. These include, for example, alkali or acid burns and ulceration, dermatitis, and general tissue inflammation. Membrane injuries can also result in exposure pathways for toxins and pathogens across the body's mucous membranes that result in secondary toxic effects or pathogenic infections;
- diseases of the kidneys (nethropathy triggered by a variety of toxins), liver, and other organs;
- diseases of the skeletal system (Itai-itai disease triggered by cadmium poisoning; fluorosis triggered by fluoride poisoning);
- unnamed combinations of asthma, coughing, shortness of breath, and tiredness;
- diseases of the central nervous system, such as: Parkinson's disease, Parkinson's dementia complex, and Lou Gehrig's disease (possibly tied to aluminum toxicity); encephalopathy (tied to poisoning from a number of metals); manganism; diminished mental capacity (lead, mercury poisoning); and encephalopathy; and
- diseases of the peripheral nervous system, including tremors, loss of motor skills, and others.

9.07.4 EXPOSURE PATHWAYS, ABSORPTION, BIODISTRIBUTION, METABOLISM, AND DETOXIFICATION OF POTENTIAL TOXINS

The types of health effects associated with exposure to a potentially toxic earth material depend upon:

- *dose response*—the intensity and duration of the exposure;
- *route of exposure*—the pathways by which exposure occurs;
- *solubility*—the degree to which the earth materials are solubilized in body fluids for a given exposure route;
- *toxicokinetics*—how potential toxins are processed in the body, including absorption, distribution, metabolism, and elimination (ADME).

Health effects of toxins can result from either local toxicity near the site of exposure or systemic toxicity in cells, tissues, and organs away from the site of exposure.

A detailed discussion of the many complex processes by which toxins are absorbed, modified, stored, and excreted by the body is far beyond the scope of this chapter. Interested readers are referred to toxicology overview volumes and texts such as Sullivan and Krieger (2001), and Klassen (2001).

9.07.4.1 Dose Response

> "All substances are poisonous, there are none which is not a poison; the right dose is what differentiates a poison from a remedy,"
>
> *Paracelsus*, 1538.

This frequently repeated quote underscores the long-recognized importance of understanding exposure intensity and duration (the dose) in assessing the health effects of potential toxins. The concept of *dose response* states that the greater amount of a toxin taken up by the organism, the greater the toxicological response (Rozman and Klaasen, 2001). However, the true determinant of toxicity is based on the concentration and form of the toxin at the site of action. The body has a remarkable capability for clearing or diminishing the toxic effects of a wide variety of toxins such as pesticides or asbestos fibers if the dose is small; toxicity results when the dose exceeds the body's inherent toxin mitigation mechanisms.

As shown by the examples in Table 2, many elements are essential to the effective functioning of the myriad biochemical processes in the body, yet can become toxic after intense exposures over short periods of time (acute toxicity) or moderately high exposures over longer periods of time (chronic toxicity). The threshold above which a material becomes toxic is a complex function of the substance, the exposure route, the chemical form of the substance as it is absorbed and presented at the site of action, and, to a lesser extent, the genetic makeup of the exposed individual (Sullivan *et al.*, 2001).

9.07.4.2 Routes of Exposure

The primary exposure pathways (Sipes and Badger, 2001) for toxins and pathogens include (see Figure 2):

- gastrointestinal tract (ingestion),
- respiratory tract (inhalation), and
- skin (percutaneous absorption).

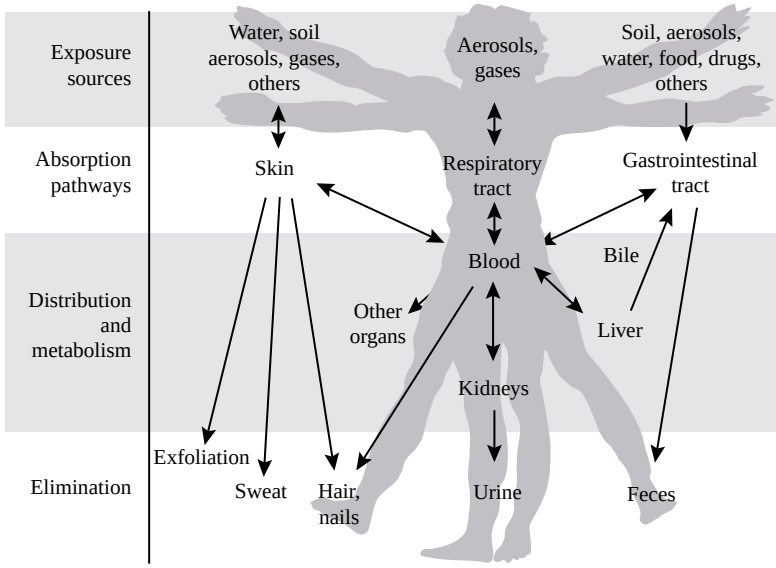

Figure 2 This schematic diagram shows the absorption pathways and systems of distribution, metabolism, and elimination for potential toxins. "Aerosols" include dusts, other solid particulates (such as smoke), and liquid droplets (such as fog, mists, etc.). Distribution may involve deposition of a toxin within a target organ and/or metabolism with or without excretion of the toxin by the target organ (after Goyer and Clarkson, 2001).

All exposure pathways can ultimately result in the absorption of soluble substances across the body's membranes (skin, eyes, respiratory, or digestive tracts), by passive or active diffusion, active transport, or cellular pinocytosis/phagocytosis (the engulfment of foreign particles by cells). The proportion of a substance in contact with a membrane that is absorbed is a complex function of many factors, including the concentration and chemical form of the substance, the relative chemical conditions ambient on either side of the membrane, and the surface area of the membrane with which the substance is in contact.

A key physiologic response when the body is exposed to foreign substances is the production of fluids at the site of exposure to help dilute, solubilize, or physically clear the substances. For example, inhalation of particulates leads to an increase in the amount of mucous and other fluids produced in the respiratory tract. Ingestion of food or other substances triggers the production of increased stomach acids to maintain the pH optimal for food digestion in the stomach.

A variety of terms have been established to help constrain the relative availability of toxins that can be readily released from administered substances into body fluids. *Bioavailability* is defined by toxicologists as the fraction of an administered dose of a substance that is absorbed via an exposure route and actually reaches the bloodstream (Ruby *et al.*, 1999; Lioy, 1990; Hamel, 1998). The *bioaccessibility* of a substance is the fraction that can be dissolved by body fluids (i.e., in the gastrointestinal tract or in the lungs), and that therefore is available for absorption (Ruby *et al.*, 1999; Hamel, 1998). Geochemists have defined *geoavailability* as the portion of a compound's total content in an earth material that can be liberated into the environment or biosphere through mechanical, chemical, or biological processes (Smith and Huyck, 1999); in a toxicological context, *geoavailability* is similar to *bioaccessibility*, but stresses the important role that the form of the toxin in an earth material plays in its overall toxicity.

For most potential toxins in earth materials, the following relationship generally holds:

$$\text{bioavailability} < \text{bioaccessibility} < \text{total concentration of a potential toxin in a substance}$$

A number of environmental regulations governing allowable toxin concentrations in materials such as soils are based on the total concentration of the toxin in the material, a parameter that is generally easiest to measure reproducibly. However, the above relationship shows that equating the total concentration of a toxin in an administered substance to its bioavailability is the worst-case scenario. This is truly valid only in the rare circumstances when the toxin is completely released from the administered substance and is in the appropriate chemical form to permit complete absorption.

As summarized by Jurinski and Rimstidt (2001), two terms have been proposed to

characterize substances that can persist in the body for many years after exposure. *Biodurability* is a measure of a substance's resistance to clearance by dissolution in body fluids. In contrast, *biopersistence* is a measure of a substance's resistance to all chemical, physical, and biological clearance mechanisms. Although these terms were specifically defined for and are most commonly applied to inhaled substances, they are also potentially applicable for other exposure routes.

9.07.4.2.1 Gastrointestinal tract (ingestion)

In general, most earth materials are ingested inadvertently, such as particles cleared from the upper respiratory tract, particles ingested by infants or small children, or particles ingested with foodstuffs (such as soil on incompletely cleaned vegetables). In the past, inadvertent ingestion of soil particles on incompletely cleaned foodstuffs actually provided humans with a substantial source of some key mineral nutrients; this source has decreased substantially due to modern advances in food processing and cleaning technologies (Taylor and Williams, 1995; WHO, 1996, Oliver, 1997). In some societies, ingestion of soil (termed geophagia) is done purposely for nutritional or cultural reasons (Oliver, 1997).

Mastication breaks down ingested earth materials into small particles, less than ~500 μm to 1 mm in diameter. This increases the surface area available for chemical reaction with the saliva and digestive juices, and may help to increase the bioaccessibility of contaminants associated with earth materials.

The fate of ingested substances is a function of their particle makeup and size distribution, their chemical solubility in the digestive fluids, the presence of other material (such as food) in the digestive tract, and biologically mediated reactions (either with or without mediation of resident microbes) that may transform the earth materials and their degradation products in the gastrointestinal tract. The survival of ingested pathogens depends on their ability to survive in the chemical conditions of the gastrointestinal tract, particularly the acidic conditions in the stomach.

Most dissolution of ingested substances occurs in the stomach, and most absorption occurs in the intestinal tract (Sipes and Badger, 2001). However, materials that are dissolved in the stomach may not all be absorbed across the intestinal tract lining. For simple diffusion across the intestinal wall into the bloodstream, a toxin must be in the most lipid-soluble (nonionized) form, which is based on its acid/base characteristics (Rozman and Klaasen, 2001). For example, a weak acid is mainly in the nonionized (lipid soluble) form in the stomach and in the ionized form in the intestine, while bases are ionized in the stomach and nonionized in the intestine. It is also possible that materials dissolved in the acidic, oxidized conditions of the stomach tract may subsequently precipitate as solids or adsorb onto solids in the intestines, due to the more alkaline and less oxygenated conditions in the intestine.

Gastrointestinal absorption, and subsequent utilization and retention by the body, of essential trace elements such as zinc, copper, and selenium can also be enhanced or diminished by the presence or absence of other trace elements and chemicals in the diet (WHO, 1996). For example, cadmium and lead absorption is enhanced when dietetic intake of calcium, iron, and phosphate is low. Phytate, an organic phosphate that is abundant in diets high in unrefined grains, especially when accompanied by high dietetic calcium, helps suppress the uptake of potentially toxic elements such as lead and cadmium, but also inhibits the uptake of essential zinc (WHO, 1996).

9.07.4.2.2 Respiratory tract (inhalation)

The health effects of inhaled earth materials are a function of the type of material inhaled (solid, liquid, gas, or pathogen); the concentration of the material in the inhaled air, the chemical composition of the material, the solubility and reactivity of the material in respiratory tract fluids, and, for solid particulates, their shape and size distribution (Newman, 2001; Sipes and Badger, 2001).

The shape and size of solid particles influence both the depth to which they can be transported in the respiratory tract and the extent to which they can be cleared by various mechanisms (Newman, 2001; Schlesinger, 1995; Snipes, 1995). The largest inhaled particles (5 μm to somewhat greater than 10 μm) are deposited in the mucous linings of the nasopharyngeal tract (Figure 2). Progressively smaller particle sizes are deposited in successively deeper portions of the respiratory tract by entrapment in a layer of mucous lining the airways. The particle-laden mucous is cleared from the trachea and bronchi in part by coughing. In addition, the cells lining the trachea, bronchi, and bronchioles are ciliated. The cilia beat to transport the particle-laden mucous up and out of the respiratory tract. Particles cleared by coughing or mucociliary clearance are either expectorated or ingested.

Particles less than ~2 μm in size reach the alveoli, the deepest portions of the lungs, where the most active exchange of oxygen and carbon dioxide occurs. These very small particles are either trapped in the alveoli or are exhaled. In the alveoli, trapped particle clearance occurs either through dissolution in the fluid lining the alveoli or through phagocytosis (engulfing of the particles) by alveolar macrophage cells. The macrophages, whose purpose is to digest or clear

respired particles, contain lysosomes with acidic pH and digestive enzymes such as acid hydrolases (Newman, 2001; Sipes and Badger, 2001; Brain, 1992). Macrophages that successfully engulf respired particulates are cleared upward in the airways, or into the lymph system or blood vessels. Another function of the macrophages, once they phagocytize particles, is to release chemicals into the surrounding epithelium that recruit other macrophages to the site to engulf other foreign particles (Lehnert, 1992).

The fate of inhaled gases in the respiratory tract is a function of the concentration of the gases in the inhaled air coupled with the solubility of the gases in the fluid lining the lungs. As summarized by Newman (2001), water-soluble gases such as sulfur dioxide tend to be absorbed at higher levels in the respiratory tract than less soluble gases such as nitrogen oxides. The greater the concentration of the gas, regardless of its solubility, the greater the likelihood that it will escape absorption in the upper respiratory tract and penetrate into the alveoli, where gas exchange with the blood is greatest.

Inhaled pathogens behave similarly to solid particulates in a physical sense. Many pathogens (such as soil fungus spores, viruses, bacteria, and bacterial spores) are in the appropriate size range to be able to penetrate to the alveoli, where they encounter warm, moist, nutrient-rich conditions that can promote pathogen development and absorption into the blood stream.

There has been increasing attention in recent years to the potential health effects of ultrafine particles less than 100 nm in diameter (see overview by Donaldson *et al.*, 2001). *In vivo* experiments with fine and ultrafine compounds of the same particles, such as metallic nickel, have shown that the ultrafine particles, for a given dose by mass, result in a greater inflammatory response than fine particles. This is probably due to the extremely small particle size and correspondingly high surface area, which are interpreted to inhibit phagocytosis, enhance oxidative stress, enhance inflammation in the lung epithelium, and permit the ultrafine particles to diffuse more readily into the lung interstitium.

9.07.4.2.3 Skin (percutaneous absorption)

Percutaneous exposures can occur either directly through the skin or through injuries to the skin. Some chemicals in gaseous or liquid form (such as methyl mercury or cyanide) can be absorbed directly through the skin. Materials that are soluble in skin perspiration can also be absorbed. Reactions of gases, solids, and liquids with the skin can lead to problems ranging from skin irritation to allergic reactions, and to chemical burns (Sullivan *et al.*, 2001). For example, contact of wet alkaline solids (such as cement or lye) with the skin can cause severe burns via a liquefaction necrosis process, which saponifies lipids, denatures proteins and collagen, and dehydrates cells. Inorganic acids (sulfuric, hydrochloric, nitric), which can form through the reaction of sulfur dioxide, hydrogen chloride, and nitric oxide gases with moisture in the respiratory tract, can cause tissue injury through dehydration and heat production that trigger denaturing of proteins and cell death. Hydrofluoric acid can trigger cell necrosis; in addition the fluoride ion can react with divalent cations in the tissues to precipitate fluoride salts that interrupt cell membrane function.

Exposure through breaks in the skin can result in the introduction of both toxins and pathogens. Toxins or toxic particles that are soluble in the blood plasma can be absorbed into the blood quite rapidly. For example, dermal exposure to chromic acid used in the electroplating industry can cause tissue damage, which then allows rapid uptake of hexavalent chromium ion and potential acute chromium intoxication.

9.07.4.3 Toxicokinetics (ADME) and Bioavailability

Toxicokinetics is the study of the time dependence of physiological processes on a toxin, and ultimately its response or effect (Boroujerdi, 2002a). The physiological processes, usually referred to as ADME, are absorption, distribution, metabolism, and elimination/excretion (Figure 3, Table 3). These are highly complex and toxin-specific. The chemical form of a potentially toxic substance, both as it is derived from an earth material and as it is transformed within the body, strongly influences its ADME as well as its bioavailability in the blood, organs, and tissues, thus dictating its toxicological effects.

Some substances are toxic at the site of exposure, because they can react chemically with the body fluids and tissues causing irritation, allergic reactions, or tissue damage. The example given previously for alkali- or acid-triggered cell necrosis via dermal exposure can also occur via respiration and ingestion exposures.

Other substances are toxic because they are not readily cleared by the body. Toxic effects of these types of substances in part result from the body's failed attempts to detoxify and/or excrete them. In addition, these substances may slowly react chemically with the body, leading to adverse effects.

The toxicity of substances that are readily soluble in the body fluids depend upon the exposure route, dose, chemical form of the substance at exposure, and processes that

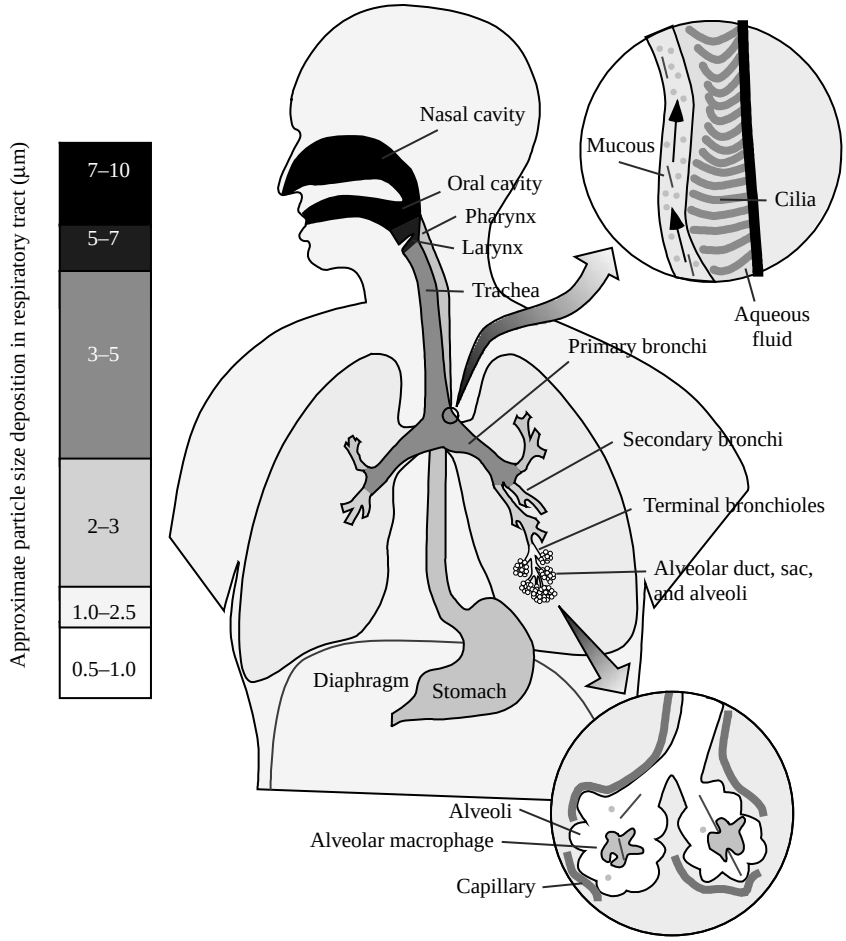

Figure 3 A schematic diagram of the respiratory system shows the fractionation of particle sizes that occurs with progressive depth in the system (after Newman, 2001).

chemically transform the substance during absorption, transport, and metabolism (Table 3). Toxicity that is dependent on the chemical form of a substance results from differences in the ways each form interacts chemically with the body.

For example, hexavalent chromium is more toxic than trivalent chromium, because it is more readily absorbed and transported across cell membranes; similar to sulfate and phosphate species, Cr(VI) can be transported via facilitated diffusion through nonspecific anion channels. Cr(VI) is readily reduced to Cr(III) in the acidic conditions of the stomach, but is less rapidly reduced in the pH 7.4 blood and tissues, through reactions with organic species such as ascorbate, glutathione, and amino acids (ATSDR, 2000b). Ingestion exposure to hexavalent chromium is therefore partly mitigated by conversion to trivalent chromium in the GI tract, where the Cr(III) compounds are less soluble, less readily absorbed, and are largely excreted in the feces. Chromium(VI) forms that are not rapidly reduced to Cr(III) are distributed by the blood to the organs and tissues, where continued reduction to Cr(III) occurs. This reduction process produces toxicity through the generation of reactive oxygen species (ROS) and reactive intermediates, which can react with and damage DNA, leading to cancer and other toxic effects. Inhalation exposure to Cr(VI) can produce toxicity in the lungs, because it is absorbed across cell membranes and is then reduced to Cr(III) within the cells. Chromium(III) that is absorbed or produced via Cr(VI) reduction is transported to the liver, where it is conjugated with glutathione and excreted in the bile. Chromium(III) species may also react to form insoluble chromium oxides.

Mercury, arsenic, and lead also provide examples of how differences in the form (valence, organic/inorganic, gas/aqueous, etc.) of a given element can result in strikingly different exposure pathways, absorption and transport mechanisms, toxicity mechanisms, metabolic processes, excretion/storage mechanisms, and the affected target organs (see Table 3).

Table 3 Biochemical mechanisms that influence the absorption, transport, storage, metabolism, excretion, and toxicity of selected potential toxins in the body.

Toxin, relative toxicities of forms, references	*Exposure pathways, absorption processes (for toxins soluble in body fluids)*	*Biochemical transport, storage, metabolism processes*	*Detoxification, excretion mechanisms*	*Source of toxicity*
Asbestos and asbestiform silicates *Amphibole asbestos, erionite > chrysotile asbestos*				
Holland and Smith (2001), van Oss *et al.* (1999), Werner *et al.* (1995), and Skinner *et al.* (1988)	*Inhalation, secondary ingestion.* Fibers are not readily cleared by macrophages, and are not completely dissolved in body fluids.	• Fibers persist in alveoli, leading to the buildup of scar tissue, and carcinogenic effects. • Fibers trigger immune response, with attack by macrophages. • Long-term chemical reactions between fibers and alveolar fluids, macrophages.	• Clearance of short fibers by mucociliary action, phagocytosis. • Some clearance by partial dissolution in lung, GI fluids.	• Incomplete fiber clearance, coupled with immune response, and macrophage death lead to scarring of lung tissue, decrease in blood oxygenation efficiency. • Release of reactive iron (and other redox-sensitive metals?) from fibers may trigger free radical generation, leading to DNA damage.
Arsenic (As) *Arsine gas > Inorganic As(III) compounds > organic As(III) compounds > inorganic As(V) compounds > organic As(V) compounds*				
Yip and Dart (2001) and ATSDR (2000a)	*Inhalation, ingestion (likely following mucociliary clearance of inhaled particles).* Easy absorption of organic forms, soluble inorganic forms. Rapid absorption of arsine gas	• As compounds bind to proteins in blood and are transported to liver, spleen, kidneys, GI tract, and other tissues or organs. • As compounds metabolized to less toxic methylated compounds in liver. • Interconversion of As(III), As(VI) forms.	• Conversion to methylated forms • Excreted in urine or stored in keratin-rich tissues such as nails, hair, skin	• As(III) reversibly binds to sulfhydryl groups, and inhibits critical sulfhydryl enzyme systems. • As(V) can also compete for phosphate in key biochemical reactions. • Chronic low-level exposure to As may stimulate growth of cells that produce keratin, leading to increased cellular division (and accompanying DNA replication) that creates allows greater opportunities for genetic damage.
Mercury (Hg) *Short-chain organic Hg (i.e., methyl, ethyl Hg) > aryl and long-chain organic Hg, inorganic Hg(II) > Hg^0*				
Yip *et al.* (2001)	*Inhalation*. Hg^0 vapor, organic Hg rapidly and efficiently absorbed. *Ingestion*. Minor Hg^0 absorption, except where mucous membranes are breached. Some absorption of soluble inorganic Hg(II). Rapid and easy absorption of organic Hg compounds due to high solubility in lipids. *Percutaneous*. Organic Hg compounds readily absorbed through skin.	• Hg^0 vapor rapidly diffuses into red blood cells and tissues, where it is oxidized to Hg(II). Some Hg^0 transported across blood-brain membrane, where it is oxidized to Hg(II). • Hg(II) distributed between plasma, red blood cells; only small amounts cross blood-brain barrier; most accumulates in renal cortex. • Aryl, long-chain organic Hg readily converted to Hg(II). • Short-chain organic Hg forms highly lipid soluble, readily cross cell membranes, placenta, and blood-brain barrier; only slowly transformed into Hg(II). Readily stored in a variety of tissues.	• Hg^0 excreted in urine, feces; some expired. • Hg(II) excreted in urine, feces; some reduction to Hg^0, which can be expired; some excretion in saliva, sweat. • Methyl Hg excreted in bile, feces, hair, and in toxic amounts in breast milk.	• Hg^0 acts as airway irritant, and cellular poison; can affect central nervous system due to ability to pass blood-brain barrier. • Hg(II) binds to sulfhydryl groups in proteins, which inhibits enzyme systems, and pathologically alters cell membranes. Strongest toxicologic effects are in the kidneys and central nervous system. • Methyl Hg toxicity primarily manifested in central nervous system, due to ability to cross blood-brain barrier.

(continued)

Table 3 (continued).

Toxin, relative toxicities of forms, references	*Exposure pathways, absorption processes (for toxins soluble in body fluids)*	*Biochemical transport, storage, metabolism processes*	*Detoxification, excretion mechanisms*	*Source of toxicity*
Lead (Pb) *Organic lead species[i.e., tetraethyl lead] > inorganic lead species*				
Keogh and Boyer (2001) and ATSDR (1999b)	*Inhalation*. Ready absorption of lead-rich fumes, volatile organic lead compounds, or soluble lead-rich particles. *Ingestion*. Absorption influenced by form, particle size, and iron and calcium absorption. More ingested lead absorbed in children than adults *Percutaneous*. Organic lead compounds readily absorbed.	• Most transport via binding to red blood cells, largely as complexes with hemoglobin, low molecular weight intracellular compounds, and membrane proteins • Distributed to bones, teeth, liver, lungs, kidneys, brain, and spleen. • Substitutes for calcium in bones; can be remobilized from bones, especially during pregnancy. • Crosses blood-brain barrier and concentrates in gray matter. • Mimics Ca in biochemical processes.	• Excretion through kidneys into urine (both dissolved and through shedding of renal tubular epithelial cells). • Possible excretion in bile.	• Affects many enzyme systems, including those critical to heme synthesis, those that maintain cell membranes, and those involved with steroid metabolism. • Also affects concentrations of neurotransmitters. Interferes with biochemical processes in the central nervous system involving calcium. • Accumulates in renal tubular cells, and interferes with other renal functions.
Chromium (Cr) Cr(VI) > Cr(III), Cr(II) > Cr^0 > Cr_2O_3 (solid)				
ATSDR (2000), and Geller (2001)	*Inhalation*. Hexavalent salts readily solubized, absorbed; metallic Cr, many Cr(III) salts less readily solubilized and absorbed; Cr_2O_3 insoluble. *Ingestion*. Cr(VI) more readily absorbed than Cr(III), but Cr(VI) can be reduced by GI fluids to Cr(III). *Percutaneous*. Cr(VI) salts can be absorbed through intact skin. Skin irritation and ulceration by Cr(VI) compounds can greatly increase absorption.	• Cr(VI) can more easily pass through cell membranes than Cr(III) — in a process similar to sulfate and phosphate species, chromate enters cells via facilitated diffusion through nonspecific anion channels. • Cr(VI) is readily reduced to Cr(III) in the body by reactions with organic acids, amino acids (i.e., ascorbate and glutathione), and microsomal enzymes. • Cr(III) may precipitate as macromolecular oxides in body fluids.	• Excreted primarily in feces and urine; minor excretion in hair, nails. • Cr(III) is conjugated with glutathione in the liver, and excreted in the bile.	• Toxicity largely results from free radicals generated during the reduction of Cr(VI) to Cr(III). • Cr(VI) has greater toxicity than Cr(III) due to its greater ability to cross membranes and bind to intracellular proteins. • Some fibrosis, pulmonary effects result from biodurability of inhaled Cr_2O_3 in lungs. • Cr(VI) salts can irritate and cause ulcers in skin, other membranes.
Cadmium (Cd)				
ATSDR (1999c) and Waalkes *et al.* (2001)	*Ingestion*. Cd generally poorly absorbed. Metal–metal and metal–protein interactions influence extent of absorption; increased sorption with iron and calcium deficiency. *Inhalation*. Cd absorbed more readily, especially from fine soluble particulates	• Absorbed Cd bound to red blood cells and serum albumin (binding to sulfhydryl groups on proteins is especially strong). • Cd bound to serum albumin is metabolized in liver through binding reactions with metallothionein, which is then released by liver to the bloodstream. Cd-metallothionen is readily taken up and stored in the kidneys. • Cd can mimic Zn in metabolic processes.	• Ingested Cd mostly remains unabsorbed in GI tract and is excreted in feces. • Absorbed Cd is excreted very slowly; therefore Cd toxicity results due to its ability to accumulate in the body.	• Above a critical threshold concentration, Cd-metallothionen is toxic to kidneys. • Cd toxicity to kidneys can lead to degradation of vitamin D metabolism, which leads to osteoporosis; Cd-induced nephotoxicity can also lead to decreased calcium and phosphate retention, which can produce osteomalacia (weakening of bones).
Zinc (Zn)				
Goyer and Clarkson (2001), ATSDR (1994), and Fisher (2001)	*Ingestion*. Zn readily absorbed in intestine. *Inhalation*. Zn can be absorbed through alveolar epithelial cells	• Zn bound to albumin in plasma, from which it can be readily liberated to the tissues. • Major tissue storage sites include liver, pancreas, bone, kidney, and muscle. • Synthesis of Zn-metallo-thionein is stimulated in the liver, which facilitates the retention of zinc by hepatocytes. • Zinc in bone is relatively unavailable for use by other tissues.	• Excreted in feces via bile and pancreatic fluids. • Zinc excretion occurs slowly (1/2 life of 300 days).	• Gastrointestinal effects if ingested. • Zinc compounds linked to some contact dermatitis • Irritation of respiratory tract • Zn linked to degenerative diseases of nervous system; may contribute to formation of degenerative plaques in brains of Alzheimer's patients.

Nickel (Ni) *Soluble Ni compounds more acutely toxic; insoluble Ni compounds more carcinogenic*				
Sunderman (2001) and ATSDR (1997)	*Ingestion*. Some soluble Ni rapidly absorbed; amount absorbed decreases if food is present in the GI tract. *Inhalation*. Ni metal is retained in respiratory system for many years, and is slowly absorbed. More rapid absorption of soluble inorganic Ni. Ready absorption of Ni carbonyl gas. *Dermal absorption*. Ni absorbed into skin (leading to local inflammatory reactions), but not absorbed through skin into blood.	• Soluble inorganic Ni bound in plasma to amino acids, low molecular weight proteins (albumin, histidine, macroglobulin, nickeloplasmin). • Storage in a wide variety of tissue sites. • In rodent studies, Ni(II) induces formation of, but does not complex with, metallothionein.	• Urine is major excretion route for absorbed Ni. • Unabsorbed ingested Ni is excreted in feces. • Some excretion via bile, sweat, salivay, hair, fingernails, milk, etc.	• Increased risk of lung, nasal cancer through inhalation exposure of sparingly soluble Ni oxides and sulfides, and soluble Ni sulfates and chlorides. • Ni may mimic or substitute for essential elements (i.e., for Ca in the hypothalamic thermoregulatory center resulting in hypothermia; for Mg and Ca in enzyme processes).
Radon (Rn)				
ATSDR (1990)	*Inhalation*. Absorption of dissolved Rn gas through alveolar lining. Some Rn gas generated by decay of inhaled radioactive particles. Daughter particles produced by Rn decay (Pb^{210}, Bi^{210}, and Po^{210}) may be absorbed as well. *Ingestion*. Primarily of Rn dissolved in drinking water.	• Rn is inert noble gas that does not interact biochemically with the blood or tissues. • Rn daughter products behave biochemically in a manner similar to that of their nonradiogenic counterparts; for example, Pb^{210} can be stored in bones.	• Most inhaled Rn exhaled as gas. • >90% of ingested Rn is distributed to the lung, where it is rapidly exhaled.	• Toxicity primarily tied to effects of radioactive decay of Rn.

9.07.4.4 Toxins and Carcinogenesis: The Role of Earth Materials

Carcinogenesis is a term used to describe the process by which a cancer-causing agent, a carcinogen, induces a heritable altered, relatively autonomous cell growth commonly referred to as a malignant neoplasm (Pitot and Dragan, 2001). Carcinogens are or form reactive intermediates, which are electrophiles or free radicals that undergo covalent reactions with cellular macromolecules containing nucleophilic sites, such as DNA (Williams and Weisburger, 1991). Ultimately, a carcinogen induces a breakdown at the cellular level by altering the replication process of cells in the cellular DNA. The process of carcinogenesis is not a single event but a series of three biological stages termed *initiation*, *promotion*, and *progression* (Pitot and Dragan, 2001).

Initiation is the initial permanent and irreversible alteration made by a chemical carcinogen on the DNA of individual cells. The process of initiation can be altered by the high efficiency of DNA repair of the cell or detoxification of the carcinogen by the metabolic processes. Furthermore, not all initiated cells survive due to the normal process of apoptosis also referred to as programmed cell death (Wyllie, 1987). Those initiated cells that do survive may continue through the stages of carcinogenesis. *Promotion* is the proliferation of initiated cells, via the induction of changes in cell shape, growth rate, and other parameters. In contrast to initiation, promotion is a reversible process and involves multiple applications of a promoting agent. *Progression* is the process by which one or more proliferations of initiated and promoted cells undergo cellular evolution to a biologically malignant cell population. Carcinogenic agents can serve as initiating, promoting, or progression agents, or as various combinations of the three.

Elements commonly found in earth materials such as nickel, arsenic, chromium, cobalt, lead, manganese, beryllium, and some of their derivatives in specific valence states have been found to be carcinogenic (Williams and Weisburger, 1991). The particular stage(s) of carcinogenesis in which these elements participate is dependent on the form and mechanism of activity for the specific element, and each can play a role in more than one or all of the three stages. Uranium, polonium, radium, and radon gas are also classified as potent carcinogens; however, their activity is mainly attributed to their radioactive properties. The mechanisms by which asbestos minerals participate in carcinogenesis are currently under debate, but they may participate in both initiation and promotion (Wylie *et al.*, 1997).

9.07.5 THE CHEMICAL CONDITIONS OF THE HUMAN BODY FROM A GEOCHEMICAL PERSPECTIVE

The chemical compositions of various human body fluids play key roles in the stability and health effects of earth materials that are taken up by inhalation, ingestion, or dermal contact. Dissolution or precipitation of solids, uptake or evolution of gases, and viability of pathogens are all dependent upon the pH conditions, oxidation states, and types of complexing agents that are present in the different body fluids. The following discussion is condensed from information found in Scanlan *et al.* (1999), Letkeman (1996), Taylor and Williams (1998, 1995), Thomas (1997, 1989), Templeton (1995), Rhoades and Pflanzer (1992), Staub (1991), Cogan (1991), May and Williams (1980), Iyengar *et al.* (1978), May *et al.* (1977), Sahlin *et al.* (1977), Altman (1961), and Gamble (1942).

9.07.5.1 Blood Plasma

Plasma is the water-rich component of the blood within which the blood cells and platelets circulate. It plays an important role in material transport, pH regulation, and other metabolic processes in the human body. Plasma interactions with earth materials are restricted to breaks in the skin and vascular system.

Plasma can be highly dynamic in its composition, depending on its location within the body (i.e., in the arteries or veins), the activities of the individual (i.e., rest or exertion, eating or fasting, etc.), and many other factors. Nonetheless, some compositional generalizations can be made.

Inorganic electrolytes are important chemical components (Table 4, Figure 4), and from a geochemical perspective comprise a near-neutral pH, sodium-chloride-bicarbonate electrolyte solution with lesser amounts of calcium, potassium, magnesium, sulfate, and phosphate. A wide variety of trace metals are also present, generally complexed with many different inorganic and organic ligands; these trace metals include silicon, iron, manganese, cobalt, zinc, copper, chromium, and selenium.

A myriad of organic species are present in plasma (Table 4), many of which form strong complexes with major cations and trace metals. High-molecular-weight proteins such as albumin, globulins, and fibrinogen comprise ~7% of the plasma and help the plasma to maintain its high osmotic pressure. Also present are: organic acids such as lactate, citrate, and tartrate; amino acids such as glycine, alanine, histidine, cysteine, and cistine; and many other organic species such as

Table 4 The chemical composition of diverse body fluids. Blank entries indicate that no data have been found to date in the literature. For entries where an average value and ranges are available, the average value is listed first, followed by the range in parentheses.

Property or constituent	*Blood plasma*	*Interstitial fluid*	*Intracellular fluid*	*Gastric fluid*	*Intestinal fluid (duodenum)*	*Intestinal fluid (upper ileum)*	*Intestinal fluid (lower ileum)*	*Sweat*
pH	7.33–7.45	7.33–7.45	7	1.5–8.4	5.8–7.6	6.1	7.23	3.8–6.5
p_{O_2}(atm)	Arterial: 0.132 Venous: 0.02–0.053							Atmospheric
p_{CO_2} (atm)	Arterial: 0.053 Venous: 0.06							Atmospheric
Calcium (mg L^{-1})	100	100	40–60	72 (21–140)	124	53 (52–54)	74 (50–98)	10–80
Sodium (mg L^{-1})	3,265	3,333	160–230	1,126 (0–2,667)	1,950–3,300	2,974 (2,423–3,303)	2,975 (2,423–3,303)	240–3,120
Potassium (mg L^{-1})	156	156	6,060–6,256	454 (20–1,270)	39–430	438 (230–1,145)	438 (230–1,145)	210–1,260
Magnesium (mg L^{-1})	24	24	316–365	22–94		228 (184–279)	228 (184–279)	0.04–2.9
Chloride (mg L^{-1})	3,580	4,041	106–248	2,750–5,640	3,052 (1,800–4,700)	4,558	4,488 (4,392–4,545)	360–4,680
Sulfate (mg L^{-1})	48	48–192	961					7–74 (“S”)
Bicarbonate (mg L^{-1})	1,647	1,709–1,892	1,709	0–1,300	475 (245–1,287)	140	890 (635–1,037)	
Phosphate (inorg, as HPO_4^{2-}, mg $L)^{-1}$	63–123	63	3,200–5,800	11.7–42	51 (47–55)	58	63	
Silica (mg L^{-1})	9.2–16.9							
Iron (mg L^{-1})	1					170 (22-177)	170 (22–177)	
Manganese (mg L^{-1})	0.0006–0.08							
Copper (mg L^{-1})	0.6–1.4							
Cobalt (mg L^{-1})	0.001–0.01							
Aluminum (mg L^{-1})	0.05–0.3							
Zinc (mg L^{-1})	0.8–6							
Protein (total, mg $L)^{-1}$)	72,000			3,300				
Albumin (mg L^{-1})	48,000							
Globulin (mg L^{-1})	23,000							
Fibrinogen (mg L^{-1})	2,800							
Bilirubin (mg L^{-1})	4				55.6 (9–180)	84.5 (12–325)	84.5 (12–325)	
Mucoprotein (mg L^{-1})				0–460				
Amino acids								
Alanate (mg L^{-1})	33			18–27	31			
Arginate (mg L^{-1})	16			33–36	29			

(continued)

Table 4 (continued).

Property or constituent	*Blood plasma*	*Interstitial fluid*	*Intracellular fluid*	*Gastric fluid*	*Intestinal fluid (duodenum)*	*Intestinal fluid (upper ileum)*	*Intestinal fluid (lower ileum)*	*Sweat*
Asparaginate (mg L^{-1})	8							
Aspartate (mg L^{-1})	1			17–23	30			
Citrullinate (mg L^{-1})	5							
Cysteinate (mg L^{-1})	3							
Cistinate (mg L^{-1})	10			18–37	45			
Glycinate (mg L^{-1})	18			13–16	17			
Glutamic acid (mg L^{-1})	7			20–30	22			
Histidinate (mg L^{-1})	13			13–20	12			
Isoleucinate (mg L^{-1})	8			7–14	11			
Leucinate (mg L^{-1})	16			12–22	12			
Lysinate (mg L^{-1})	26			14–18	22			
Methionate (mg L^{-1})	4			8–15	20			
Phenylalanate (mg L^{-1})	11			8–18	17			
Prolinate (mg L^{-1})	24			17–32	30			
Serinate (mg L^{-1})	13			16–23	20			
Threoninate (mg L^{-1})	20			15–25	18			
Tryptophanate (mg L^{-1})	2			14–19	11			
Tyrosinate (mg L^{-1})	10			10–11	5			
Organic acids								
Citrate (mg L^{-1})	22							
Lactate (mg L^{-1})	164							
Malate (mg L^{-1})	4							
Oxalate (mg L^{-1})	1							
Pyruvate (mg L^{-1})	8							
Salicylate (mg L^{-1})	1							
Succinate (mg L^{-1})	5							
Ascorbate (mg L^{-1})	8			10				
Cholic acid (mg L^{-1})					1,300–4,600			
Glucuronic acid (mg L^{-1})				20				
Sialic acid (mg L^{-1})				73.1				
Histamine (mg L^{-1})				0.013–0.535				
Urea (mg L^{-1})	50.4			20				
Glucose (mg L^{-1})				3.5–12				
Fucose (mg L^{-1})				138				
Hexosamine (mg L^{-1})				327				

Sources: Altman (1961), Scanlan *et al.* (1999), Thomas (1997, 1989), May *et al.* (1977), Gamble (1942), Iyengar *et al.* (1978), Letkeman (1996), and Rhoades and Pflanzer (1992).

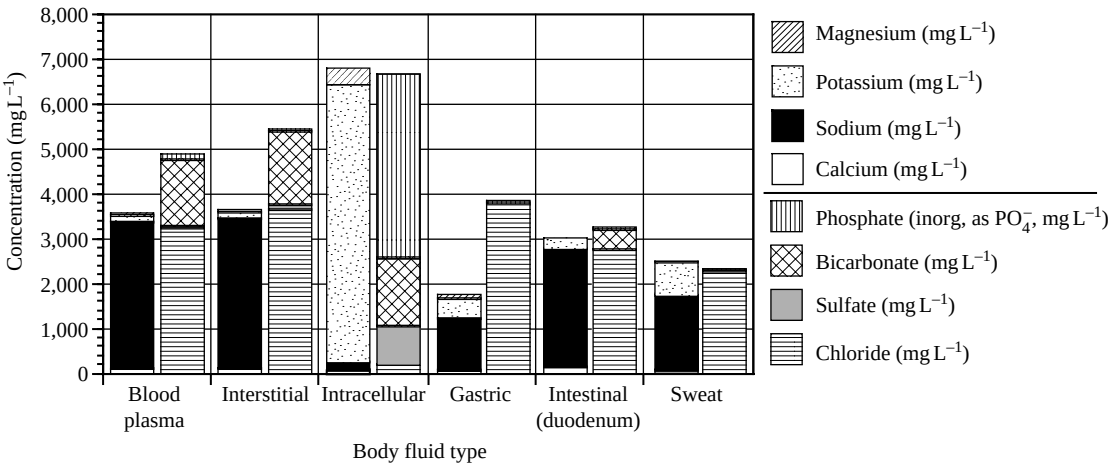

Figure 4 Concentrations of the major inorganic electrolyte species can vary substantially between the different body fluid types. These variations likely play an important role in the relative stability of a variety of minerals and earth material components in the body's different body fluid types. For a given fluid, cations are shown on the left, anions on the right.

peptides (i.e., glutathione), sugars (glucose and others), and fatty acids.

In order to sustain life and optimize the many biochemical reactions crucial for effective physiological function, the body strives to maintain its pH in the narrow range between 7.35 and 7.45 using a complex array of inorganic and organic buffers in the plasma and interstitial fluids. Excess hydrogen ions, such as lactic acid produced during exercise, are first buffered by reaction with bicarbonate ions in the plasma, producing dissolved CO_2 that is then removed as exhaled gas. The kidneys can also remove excess CO_2 through excretion of carbonic acid in the urine. If CO_2 is produced faster than it can be removed by ventilation or the kidneys, the body must turn to nonbicarbonate buffers in the blood, including hemoglobin, organic and inorganic phosphates, and plasma proteins.

Oxidation–reduction conditions (Figure 5) and processes in the plasma may be influenced by a wide variety of potential inorganic and organic redox buffers. Various organic redox couples that may be active, such as reduced/oxidized glutathione, ascorbic acid-dehydroascorbic acid, and cysteine-cystine, all have relatively reduced redox potentials in the vicinity of −100 mV to 0 mV; hence the overall Eh of the plasma is generally assumed to be in this range. Partial pressures of oxygen in arterial ($P_{O_2} = 0.132$ atm) and venous ($P_{O_2} = 0.02–0.053$ atm) plasma indicate that the plasma has, even in its most oxygen-depleted state in the veins, high dissolved oxygen concentrations that are well out of redox equilibrium with organic redox buffers and with all of the carbon-rich compounds found in the blood and tissues. A variety of redox-sensitive elements such as sulfur and iron can also be out of redox equilibrium, both internally (i.e., between reduced and oxidized forms of the same element) and externally with dissolved oxygen in the plasma. For example, various amino acids, glutathione, and proteins such as metallothioneins contain reduced sulfur in the form of sulfhydryl (HS) groups, but are common in plasma that is sulfate-rich. Hemoglobin, a protein, contains tightly bound ferrous iron, even though the iron atoms in hemoglobin are those with which transported oxygen associates or dissociates.

By exploiting a variety of complex chemical reactions involving proteins and other organic species, the body can selectively oxidize or reduce specific redox-sensitive elements in the plasma and the tissues as needed to meet its physiologic needs. For example, iron is routinely shifted between oxidation states by the action of specific enzymes and other organic compounds. When macrophages destroy aged blood cells and recycle hemoglobin, the ferrous iron in the hemoglobin is oxidized to ferric iron, which then combines with globulin proteins to produce transferrin. Transferrin carries the iron to storage sites such as the liver (where the iron is stored in oxidized form within the protein ferritin) or the bone marrow, where hemoglobin and the red blood cells are produced. Mobilization of iron from the ferritin stores, transport of iron across cell membranes, and production of heme (the iron-rich portion of hemoglobin), requires reduction of the ferric iron to ferrous iron, through the action of specific enzymes and other organic compounds such as flavins.

9.07.5.1.1 Chemical complexing in the plasma

The solubility of major cations, trace metals, and metalloids in the plasma is enhanced by

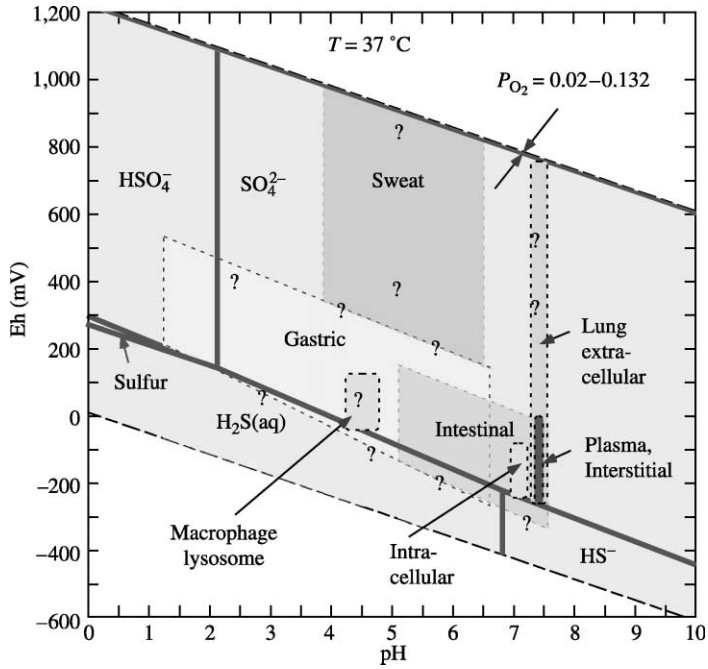

Figure 5 A plot showing variations in pH and speculated variations in Eh further illustrates the variability between different body fluid types. For comparison, the light gray area shows the Eh–pH stability field for water, the medium gray lines mark the stability fields of major inorganic sulfur species, and the darker gray line along the upper stability limit for water shows the range of Eh values in equilibrium with dissolved oxygen at arterial (upper edge of area) and venous (lower edge of area) oxygen pressures. The Eh ranges for the various body fluid types are highly speculative, and are postulated based on comparison to inferred Eh values for the plasma (black area) (see discussion in text). While there are indications that most body fluids have an overall Eh that is quite reduced and well out of equilibrium with dissolved oxygen in the plasma, there are substantial uncertainties in the extent to which the different potential redox couples in the body fluids reach equilibrium with each other and, especially in the case of sweat and lung fluids, dissolved oxygen.

complexation reactions with inorganic and, especially in the case of the trace metals, organic ligands in the plasma. Cation and metal species are distributed between several different states in the body:

- *Solids.* For example, calcium and chemically similar trace metals (such as lead, cadmium, and uranium) are incorporated into the phosphate phases of the teeth and bones.
- *Relatively inert or thermodynamically irreversible high-molecular-weight proteins.* These include, for example, the metal-binding proteins such as metallothioneins (including ceruloplasmin, a copper protein, and α_2 macroglobulin, a zinc protein), ferritin, and hemoglobin. Metals tend to be bound irreversibly to these proteins, and so are generally unavailable for participation in chemical reactions with other species.
- *Labile proteins.* These include proteins such as transferrin (which complexes iron, as discussed previously) and albumin (which complexes copper, zinc, and other metals).
- *Labile low-molecular-weight amino acids and organic acids.* These include, for example, complexes with amino acids such as cysteine and histidine, complexes with carboxylic acids such as lactate, and mixed ligand complexes involving more than one amino acid or carboxylic acid.
- *Labile inorganic complexes or aquated metal ions.* These include complexes with bicarbonate and chloride ions, and rarer hydroxy complexes.

In general, the latter three forms are viewed as those between which metals can be exchanged most readily in response to changing chemical conditions in the body. However, cations and metals can be mobilized under certain conditions from bones and other solids to the plasma, and can also be released from high-molecular-weight proteins if the proteins are degraded through disease or normal recycling mechanisms.

The chemical speciation of the different cations and metals strongly influences their chemical and physical behavior in the plasma and tissues. For example, chemical species with net neutral charges are most easily transferred across cell membranes and other membranes, and so are most readily absorbed by the body. Due to limitations in

current chemical analysis techniques that preclude measurement of the actual concentrations of many complexes, thermodynamic-based speciation calculations have been used to estimate which complexes are predominant for a given metal, and whether or not their net charge will be amenable for their uptake across membranes into the body. Such calculations, although fraught with potentially substantial uncertainties in the thermodynamic data, etc., illustrate that each of the major cations and trace metals in plasma is probably complexed by a unique mix of ligands (Figures 6 and 7). The trace metals are most strongly complexed by amino acids, mixed ligand complexes with multiple amino or carboxylic acids (such as copper-cystinate-histidinate), and glutathione (Figures 6 and 7).

9.07.5.2 Interstitial Fluids

Interstitial fluids bathe the cells and tissues. With respect to the electrolytes and other constituents, physiology textbooks indicate that the interstitial fluids are generally similar in composition to the plasma, with the important

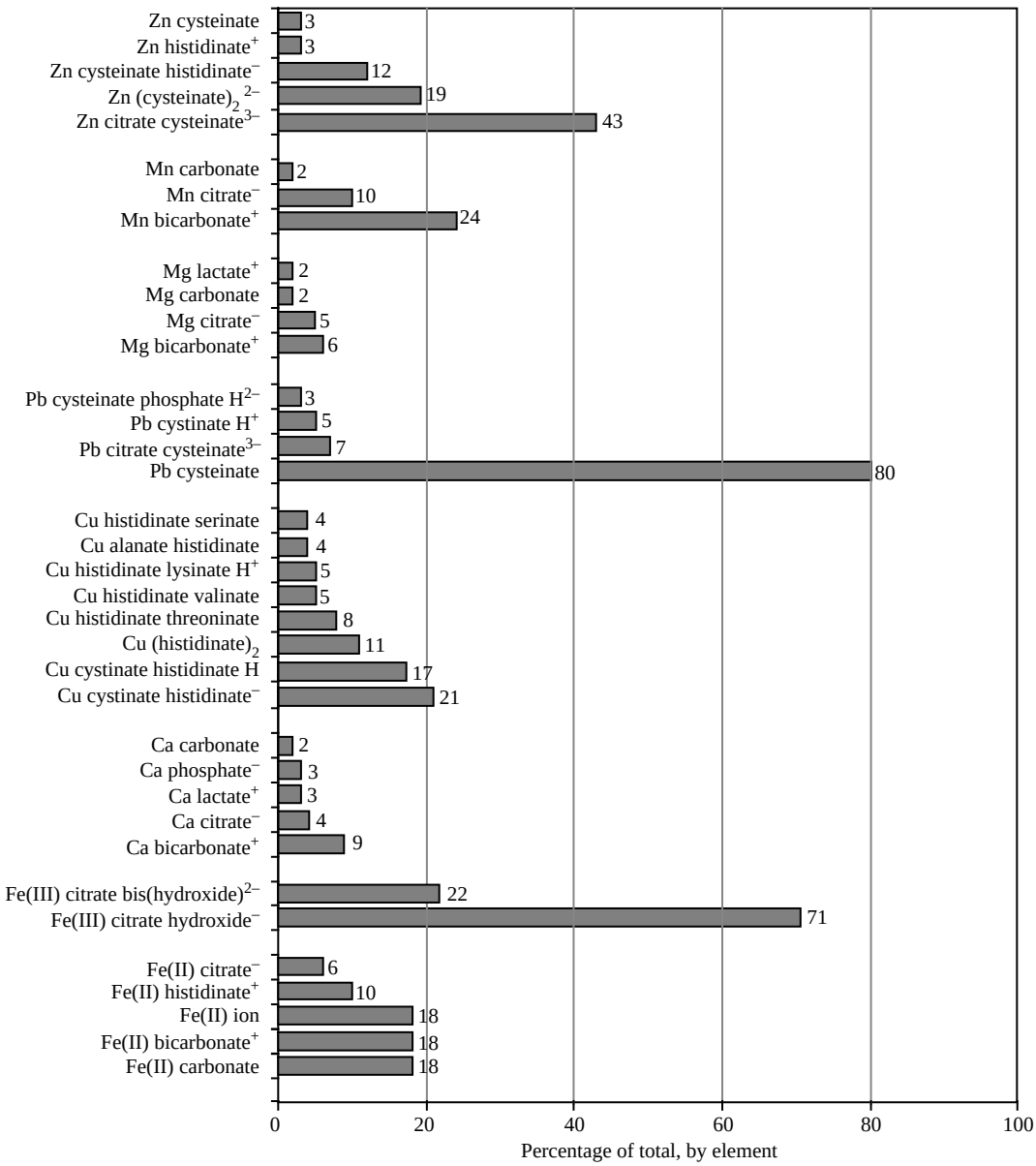

Figure 6 Chemical speciation calculations have been used (May *et al.*, 1977; May and Williams, 1980) to estimate the dominant low-molecular-weight organic and inorganic complexes for various metals in the plasma. The results show that each metal can be complexed by a unique set of ligands. Results of such speciation calculations can be used to infer the important chemical complexes and complexing ligands in other body fluids such as extracellular fluids.

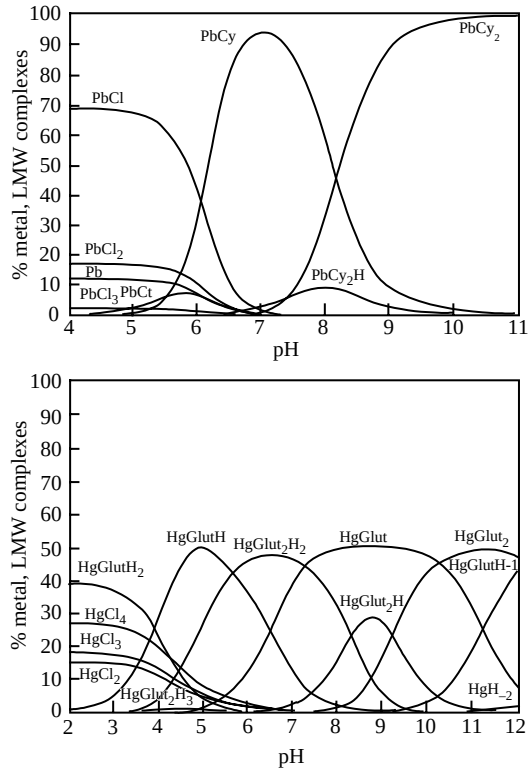

Figure 7 Letkeman (1996) used chemical speciation calculations to estimate the major complexes for lead and mercury as a function of pH in a fluid having overall plasma composition. The results show that most metal complexes with low-molecular-weight organic ligands such as amino acids diminish in importance with decreasing pH (such as in the gastric fluids) due to the increased protonation of the organic ligands. Cl—chloride; Cy—cysteinate; Ct—citrate; Glut—glutathione (reproduced by permission of the Division of Chemical Education Inc. from *J. Chem. Educat.* **1996**, *73(2)*, 165–170).

exception that they contain much lower concentrations of proteins (such as albumin and globulin) than the plasma (Table 4; Figures 4 and 5).

9.07.5.3 Intracellular Fluids

Intracellular fluids (also called the cytosol) are quite different compositionally from plasma and interstitial fluids (Table 4, Figures 4 and 5). The internal pH of many cells is maintained near 6.9–7.0. via various membrane transport mechanisms such as Na^+/H^+ and Cl^-/HCO_3^- exchangers, and various phosphate and protein buffers. In contrast to the plasma, the intracellular fluids have substantially lower concentrations of sodium, calcium, chloride, and bicarbonate and higher to substantially higher concentrations of potassium, magnesium, sulfate, inorganic and organic phosphates, proteins, and other organic species. The cells maintain their high K/Na via the sodium pump, also known as the Na^+/K^+ ATPase pump; the free energy derived from the hydrolysis of ATP to ADP is used to drive the transport of sodium out of the cell and potassium into the cell.

The redox potential within the cells is "substantially lower" than in the plasma (May and Williams, 1980), and may vary depending upon particular cellular biochemical activities and a myriad of potential redox couples such as reduced and oxidized glutathione species. In general, greater levels of reduced glutathione in the intracellular fluids than in the plasma may provide an indication of an overall lower oxidation condition within the cells. However, it is interesting to note that intracellular fluids have relatively high concentrations of dissolved sulfate (Table 4), in spite of the more reduced conditions inferred to be present.

The deleterious effects of toxins and processes that cause shifts in the redox balance within the cells are thought to lead to tissue damage and disease such as cancer. For example, generation of reactive superoxide and hydroxyl radicals by the intracellular reduction of metals such as Fe(III) (when present in excess of the amounts needed for proper cellular function) and Cr(VI) is thought to lead to cell membrane damage, destruction of enzymes and other proteins (through oxidation of sulfhydryl groups), and induction of breaks in DNA strands (Kawanishi, 1995; Rhoades and Pflanzer, 1992; Aust and Lund, 1990). Chemical species such as glutathione, ascorbic acid, and selenium, and enzyme systems such as catalase are examples of the chemicals that the body mobilizes to scavenge free radicals, but adverse effects occur when the free radicals are generated in excess and these defense mechanisms are overwhelmed (Kawanishi, 1995).

9.07.5.4 Gastrointestinal Fluids

The chemical composition of gastric fluids can vary substantially depending upon the presence or absence of food in the stomach. Under fasting conditions, the pH of gastric fluids is around 1.5, and their electrolyte composition is essentially that of a hydrogen-sodium-chloride solution with lesser amounts of potassium, calcium, and magnesium (Table 4; Figure 4). Organic species present in the gastric fluids include a wide range of amino acids, carboxylic acids, mucoproteins, other proteins, carbohydrates, and enzymes such as lipase, lysozyme, and pepsin that catalyze the breakdown of proteins and other components of food. As food is added to the stomach, the pH of the gastric fluids increases substantially due to

neutralization by the food. In addition, the concentration of species such as bicarbonate, proteins, and amino acids increases due to the neutralization of the gastric acid and the chemical breakdown of the food. In addition, other components such as tannins and humic acids can be added to the gastric fluids from ingested food, drink, and other materials.

The redox conditions of the gastric fluids are probably quite variable, depending upon the dissolved oxygen content and the rates at which different organic redox couples reach equilibrium (Figure 5). Oxygen pressures may transiently reach near atmospheric (due to air swallowed with food or drink) but are probably shifted to substantially lower levels as food is digested and the oxygen in swallowed gases is consumed chemically. The fact that Cr(VI) is readily reduced to Cr(III) in the stomach (Table 3) provides indications that reduced conditions can be achieved in the stomach, and that redox couples active in the gastric fluids are probably not in redox equilibrium with dissolved oxygen.

Cation and metal speciation is likely to be substantially different in the gastric fluids than in the plasma, with decreased complexation with organic acids (due to increased acid protonation) and increased speciation as hydrated ions and chloride complexes (Figure 7).

Fluid secretions in the upper (duodenal) portion of the small intestine are alkaline, and help raise the pH of the partially digested food–gastric juice mixture called chyme (Table 4). Bile salts and pancreatic fluids are added to the chyme in the upper portions of the intestine. Bile aids in the digestion and absorption of lipids, whereas the pancreatic fluids contain enzymes and other organic species that assist with the continuing breakdown of proteins and carbohydrates. Redox conditions in the intestinal tract, although not specified in detail in the literature, are possibly somewhat more reduced than those generally present in the stomach, due to the increased separation from the periodic influx of atmospheric oxygen during swallowing. Metal complexes with amino acids and carboxylic acids probably increase in importance as the chyme moves into the intestine where its pH increases. Some metals may precipitate or sorb onto solids in the higher-pH environment of the intestine.

9.07.5.5 Extracellular Lung Fluids

Fluids lining the deeper portions of the lungs are a complex and dynamic mixture of several components (Goerke, 1998; de Meringo *et al.*, 1994; Scholze and Conradt, 1987; Reynolds and Chretien, 1984; Kanapilly, 1977; Gamble, 1942). *Surfactants* are composed predominantly of phospholipid-protein material such as dipalmitoyl phosphatidylcholine. They help the lungs lower their surface tension, maintain a wet surface for gas exchange, and reduce the amount of muscular effort needed to expand the lungs. *Mucus material* (composed primarily of glycomucoproteins) helps trap and clear foreign particles. An *aqueous serum transudate* phase helps with gas transport.

A variety of literature sources that discuss simulated lung fluids (SLFs) imply that the aqueous component of lung fluid is an electrolyte fluid generally similar in composition to that of interstitial fluid with pH near 7.4 (Table 4). Redox conditions in the lung fluids are not readily available from the literature. It is unclear which organic redox couples are active in the pulmonary fluids, and how these may drive redox equilibria to lower Eh values than those in equilibrium with the 0.132 atm PO_2 present in the alveoli.

9.07.5.6 Fluids in the Alveolar Macrophages

Once an alveolar macrophage engulfs a particle, the resulting phagocytic vacuole fuses with lysosomes to form a phagolysosome, within which the particle is digested. Respired foreign particles can therefore also come into contact with both macrophage cytoplasm and lysosomal fluids (Collier *et al.*, 1992). Some studies indicate that alveolar macrophages maintain a substantially lower pH in their intracellular fluids than most cells, from 3 to 4 (van Oss *et al.*, 1999; de Meringo *et al.*, 1994; Hume and Rimstidt, 1992; Jaurand *et al.*, 1984), whereas others report macrophage intracellular fluid pH values in the 6.5–6.9 range (Collier *et al.*, 1992). Electrolyte concentrations in the macrophage intracellular fluids, or cytosol, are inferred to be grossly similar to intracellular fluids of other types of cells (Table 4), with possible variations arising depending upon the cell function.

Compositions of lysosomal fluids in the alveolar macrophages have been characterized primarily in terms of their high concentrations of proteases, bactericidal enzymes such as lysozyme, and other cytotoxic chemicals (Burns-Naas *et al.*, 2001; Brain, 1992). The pH of lysosomal fluids is generally thought to be low, in the range from 4 to 5 (Collier *et al.*, 1992; Nyberg *et al.*, 1992; Johnson, 1994). These chemical features are designed to help the alveolar macrophages degrade foreign particles that they engulf.

9.07.5.7 Sweat

Sweat can vary substantially in composition depending upon activity level and other parameters (Table 4). For example, the pH can

vary rather widely between 3.8 and 6.5. The dominant electrolytes in sweat are sodium, chloride, and phosphate. Urea, ammonium, and lactate, generated as metabolic wastes, are abundant, and a variety of amino acids are also present. Although sweat on the skin surface is most likely saturated with oxygen at atmospheric pressure, it is again unclear the extent to which various organic redox couples may shift redox equilibria to more reduced conditions.

9.07.5.8 Summary—Body Fluids from a Geochemical Perspective

As summarized in Table 4 and Figures 4–7, various human body fluids with which earth materials may come into contact exhibit a wide range of compositions, including their pH and Eh, electrolyte content, and concentrations of organic species such as amino acids, organic acids, and proteins. This compositional variability indicates that any given mineral or earth material, and its contained metals, may potentially behave quite differently from a geochemical perspective depending upon the exposure pathway, the resulting body fluid(s) it encounters, and how it may modify body fluid chemistry.

9.07.6 METHODS USED TO ASSESS THE INTERACTIONS OF EARTH MATERIALS WITH, AND THEIR TOXIC EFFECTS UPON, THE HUMAN BODY

There is a wide variety of chemical and toxicological methods that are used to assess the body's interactions with earth materials and their potential toxic effects. These can be grouped into several major categories, including: *in vitro* bioaccessibility and biodurability tests; *in vitro* toxicological tests; *in vivo* toxicological tests; *in vivo* bioaccessibility tests; and computer-based chemical modeling calculations. Due to length limitations, only a brief overview of the extensive literature available on these topics is possible in this chapter; a more detailed bibliography is available from the authors upon request.

Bioaccessibility tests (also called bioavailability or physiologically based extraction tests) have been used extensively to measure the short-term solubility of and metal extraction from earth materials and other substances in simulated gastric, intestinal, and lung fluids (Ruby *et al.*, 1992, 1996, 1999; Hamel, 1998; Battelle and Exponent, 2000; Oomen *et al.*, 2002; Mullins and Norman, 1994). *Biodurability* tests have been used extensively to measure the long-term solubility of earth materials and other substances such synthetic glass fibers in SLFs (Johnson and Mossman, 2001; Jurinski and Rimstidt, 2001; Werner *et al.*, 1995; Mattson, 1994a,b; Eastes *et al.*, 1996, 2000a,b). The goal of both types of tests is to understand the types and rates of chemical dissolution or alteration reactions that earth materials and other substances might undergo in the body via various exposure routes. The studies can vary considerably in their physical design; particle size, shape, and other characteristics of the minerals tested; fluid compositions; test duration; and other parameters. Key uncertainties that are inherent in both types of *in vitro* solubility-based tests are (1) how well they reproduce actual conditions in the body; and (2) how well the predicted results (such as particle dissolution rates, or types and relative abundances of trace elements solubilized from the particles) can be readily extrapolated to infer toxic responses *in vivo* (de Meringo *et al.*, 1994; Ruby *et al.*, 1999; Johnson and Mossman, 2001). Nonetheless, even the least sophisticated tests may provide at least some valuable information to the investigator regarding chemical reactions that may be occurring between the particles and fluids *in vivo*; this is especially true when the test results are interpreted in an appropriate mineralogical and geochemical context.

A variety of *in vitro* toxicity tests have been developed to model the effects of toxins on living cells or tissues. In these tests, a carrier medium (such as fetal bovine serum) containing given concentrations, or doses, of a particular toxin are added to cell cultures (cell lines). Various indicators of toxicity, cell morphology transformation, or cell proliferation are then measured after specified periods of time. The cell types used in a particular study can be chosen to approximate the types of cells that would be affected during actual exposure, such as respiratory cells or tissues. Toxicity indicators include, for example, measures of the percent of viable cells remaining at the end of the test (compared to a control line with no added toxin), and the concentrations various cytokines or other cytoplasmic enzymes induced from the cells by the toxin. Uncertainties with the *in vitro* toxicity tests include how comparable their results are to those of *in vivo* toxicity tests, and how well they reproduce actual physiological conditions and processes in the human body (Johnson and Mossman, 2001).

In vivo toxicity tests involve the direct exposure (via appropriate exposure routes) of living animals to variable doses of toxins over time, followed by measurement of toxic effects or exposure indicators. Inhalation tests either expose the subject animals to known concentrations of particles in an airstream, or utilize direct intratracheal implantation of the particles in the subject animals (e.g., studies summarized in Johnson and

Mossman, 2001; Buchet *et al.*, 1995). Ingestion tests usually provide the subject animals with a diet containing known concentrations of the target earth material being ingested (Ruby *et al.*, 1996; Schoof *et al.*, 1995). Examples of toxic effects that have been assessed include adverse changes in neurological or other physiological behavior in response to the exposure, the occurrence and severity of abnormal changes in pathologic tissue samples, such as fibrosis, tumor growth, or cell necrosis, measures of exposure and absorption such as metal concentrations in blood, urine, fur, or nails (Schoof *et al.*, 1995; Buchet *et al.*, 1995; Ruby *et al.*, 1996), and the burden and nature of foreign materials in lung tissues or other tissues (Churg *et al.*, 1989). An important uncertainty is how well the physiologic processes and endpoints of exposure, dose/response, toxin uptake, and toxicity measured in the *in vivo* tests on animals can be extrapolated to quantify similar processes and endpoints in the human body.

In vivo bioaccessibility (bioavailability) assessments are often conducted on individuals exposed to potential toxins to assess the extent to which the toxins have been absorbed, transported, and metabolized by the body. Bioavailability can be calculated as the fraction of the exposure level (dose) that reaches the systemic circulation (Boroujerdi, 2002b). The extent of absorption is determined by comparing the plasma concentration following a single intravenous administration to those following the primary exposure routes (Medinsky and Valentine, 2001). Such *in vivo* analyses can assess the whole body bioaccumulation of the material of concern as well as the particular tissues in which this deposition takes place. These models have been useful in toxin evaluation and are presently being used by some federal agencies in extrapolating experimental data to human risk situations (Pitot and Dragan, 2001).

Aqueous chemical speciation calculations (Alpers and Nordstrom, 1999; Bethke, 1996) have been used for some time to help understand the speciation of and trace metal chelation in diverse human body fluids such as plasma, wound fluids, saliva, sweat, fat emulsions, and gastrointestinal fluids (Taylor and Williams, 1995, 1998; Williams, 2000). In contrast, chemical speciation calculations have only been used infrequently in studies evaluating interactions between the human body and earth materials such as asbestos (Hume and Rimstidt, 1992; Gunter and Wood, 2000; Taunton *et al.*, 2002; Davis *et al.*, 1992, 1996). There are many potential uses of chemical speciation calculations in the interpretation of interactions between human body fluids and earth materials. For example, the interpretation of *in vitro* mineral solubility tests could be greatly improved by chemical speciation calculations on the resulting leach fluid. Comparison of the chemical compositions of many simulated body fluids used in *in vitro* extraction tests to results of chemical speciation calculations of the plasma and other body fluids (May *et al.*, 1977) indicates that the simplified simulated fluid compositions used in most studies may not include a broad enough array of organic ligands, especially those that are the most effective metal complexing agents (such as cysteine and glutathione). As a result, the *in vitro* tests may understate the true metal mobility from earth materials.

Chemical reaction path calculations (Alpers and Nordstrom, 1999; Bethke, 1996) have only seen limited use as applied to fluid-mineral interactions in the human body (e.g., Davis *et al.*, 1992). The potential further applications in this realm are intriguing, both for understanding chemical reactions between body fluids and earth materials, and in understanding potential changes in body fluid chemistry in response to physiological processes and therapeutic treatments such as toxic metal chelation therapy.

9.07.7 EARTH MATERIALS IN A BIOSOLUBILITY AND BIOREACTIVITY CONTEXT

Important geochemical factors that influence the health effects of earth materials (Figure 8) are: (i) their *biosolubility*, the extent to which they are soluble in the various body fluids (their) and (ii) their *bioreactivity*, the extent to which they can modify key body fluid parameters such as pH, concentrations of major electrolytes, and redox species. As discussed previously, *biodurable* minerals and earth materials are those that are generally bioinsoluble or sparingly biosoluble in body fluids, and so cannot be cleared rapidly by chemical dissolution. *Bioaccessible* earth materials are those that are readily biosoluble (and therefore can readily release toxins into the body fluids by their dissolution), or that may not be biosoluble but that contain readily bioaccessible toxins (e.g., heavy metals sorbed onto particle surfaces). A given earth material may vary in its biodurability or bioaccessibility depending upon the exposure route, due to differences in its solubility or toxin bioaccessibility in the particular body fluids present. Especially in the case of biodurable earth materials, geochemical processes controlled by particle surface chemistry and phenomena may be quite important in influencing dissolution rates (Guthrie, 1997; Hochella, 1993).

Earth materials with abundant soluble alkali components (such as cement or concrete) or acidic

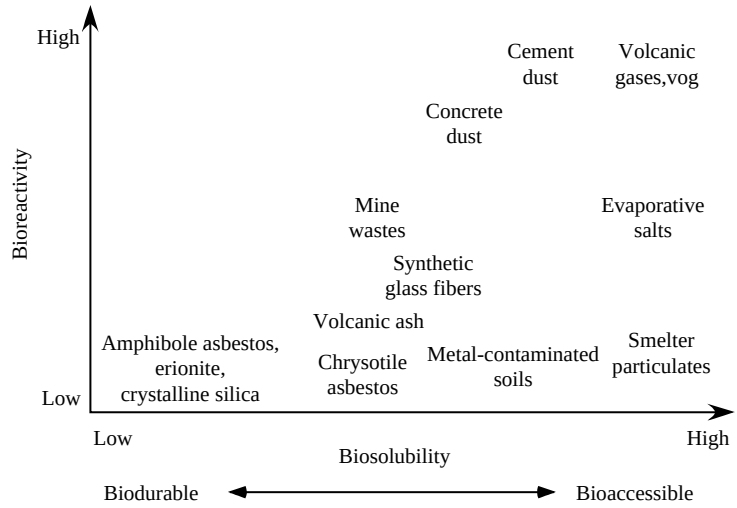

Figure 8 This schematic plot shows the inferred biosolubility and bioreactivity of general classes of earth materials. Many types of earth materials (i.e., mine wastes, volcanic ash, soils) can contain a complex variety of minerals having quite different biosolubilities and bioreactivities, so the particular location of a given earth material on the plot should be considered as an averaged approximation.

components (such as acid volcanic gases, or acid-generating salts in mine wastes) are the most bioreactive. However, even sparingly soluble, biodurable earth materials such as asbestos can be somewhat bioreactive by slowly reacting at their surfaces with, and releasing chemicals into, the surrounding fluids and tissues.

9.07.8 THE MEDICAL GEOCHEMISTRY OF BIODURABLE EARTH MATERIALS

Adverse health effects of biodurable earth materials result primarily from inhalation exposure to airborne particulates. The earth materials that are most commonly associated with adverse respiratory health effects include dusts of asbestos, erionite (a fibrous sodium-rich zeolite), crystalline silica, and coal. However, dusts from a wide variety of other biodurable earth materials (such as metal oxides, talc, kaolinite, feldspars, bentonite, fuller's earth, and micas) and non-earth-materials (such as wood dusts, wood fibers, glass fibers, and others) are also known to be associated with adverse health effects if exposures are of sufficient intensity and duration. Adverse health effects resulting from ingestion and percutaneous exposure to biodurable earth materials (either direct or indirect of particles cleared from the respiratory tract) have also been the focus of some investigation and speculation. After decades of research, there is a substantial and growing understanding of the important role that geochemical processes play in the health effects of biodurable minerals. However, there are still many areas in which conflicting information and interpretations reveal continuing uncertainties.

9.07.8.1 Asbestos, Erionite, and Other Fibrous Materials

Many different epidemiological and toxicological studies during the last several decades have shown that intense, generally prolonged inhalation exposure to asbestos and erionite is associated with elevated occurrences of diseases such as asbestosis, lung cancer, pleural effusions, pleural thickening, pleural plaques, and mesothelioma cancer. Although chrysotile asbestos, amphibole asbestos, and crionite fibers all can generate adverse health effects such as fibrosis, there is a recognition that the different forms are not equal in their pathogenicity, with amphibole asbestos and erionite considered as more pathogenic than chrysotile asbestos. See summaries in Nolan *et al.* (2001), Holland and Smith (2001), and Guthrie and Mossman (1993). No definitive links have been established between asbestos exposure and gastrointestinal health effects (Holland and Smith, 2001).

Most attention has focused on occupational exposures to chrysotile and amphibole asbestos as it has been mined, processed, and used commercially or industrially. However, there has been some renewed attention to potential occupational, residential, and environmental exposures to asbestos that occur as an accessory mineral in rocks such as serpentinite (Renner, 2000), and to deposits of other industrial minerals such as vermiculite (e.g., Libby, Montana: Lybarger *et al.*, 2001; Dearwent *et al.*, 2000; McDonald *et al.*, 1986; Wright *et al.*, 2002; Van Gosen *et al.*, 2002; Meeker *et al.*, in press; Wylie and Verkouteren, 2000). Environmental exposures to erionite have also been well documented as

the cause for asbestos-related disease (studies summarized in Ross *et al.* (1993); Dumortier *et al.* (2001)).

9.07.8.2 Crystalline Silica

Crystalline silica includes the silica minerals quartz and its polymorphs such as cristobalite and tridymite, which have the same chemical formula but different crystal structures. Amorphous, noncrystalline silica can also occur in a wide variety of geologic environments (Ross, 1999).

Silicosis, a form of pulmonary fibrosis, is the primary health problem resulting from inhalation exposure to particles of crystalline silica (SSDC, 1988; NIOSH, 2002; Castranova, 2000; Castranova and Vallyathan, 2000). Other diseases associated with occupational inhalation exposure to crystalline silica include lung cancer, chronic obstructive pulmonary disease, nonmalignant respiratory disease, auto-immune related diseases (such as rheumatoid arthritis), renal diseases, and (as a complication of silicosis) increased risk of bacterial or fungal infections such as tuberculosis. Skin granulomas or obstructive lymphopathies may result from dermal exposure and uptake of silica particles (NIOSH, 2002).

9.07.8.3 Factors Influencing the Health Effects of Biodurable Minerals

9.07.8.3.1 Particle shape and size

During inhalation, fibrous particles with length generally less than 10–20 μm and diameters less than 0.5–1 μm are thought to flow aerodynamically into the deep alveoli, where they can lodge (Holland and Smith, 2001). Because the alveolar macrophages are not big enough to completely engulf these fibers, macrophage clearance of the fibers is limited. Various studies indicate that short fibers are less pathogenic than long fibers, in part because the long fibers are less readily cleared than the short fibers (Holland and Smith, 2001; van Oss *et al.*, 1999; Davis *et al.*, 1991), and possibly in part because of chemical differences between short and long fibers (Graham *et al.*, 1999). Fibers that are needle-like and rigid (van Oss *et al.*, 1999) may also physically penetrate the lung tissue, where they can then be transported by the lymph system or can physically migrate to the pleural or peritoneal spaces (Holland and Smith, 2001). Some reports conclude that amphibole fibers (which tend to be more straight and rigid than typically curved chrysotile fibers) are more likely to be able to penetrate deeper into the lung tissue than chrysotile fibers, and therefore are more likely to contribute to interstitial diseases such as mesothelioma (i.e., van Oss *et al.*, 1999). However, some recent studies indicate that short chrysotile fibers (less than ~5 μm) may also be able to penetrate and migrate to the pleural and peritoneal spaces, and can therefore also trigger mesothelioma and other diseases in these regions (Suzuki and Yuen, in press, 2001).

Crystalline silica particles (except for fibrous crystobalite and tridymite) tend to be more equant in shape rather than fibrous, and therefore small (<1.5–2 μm) particles that lodge deep in the respiratory system should be relatively amenable to macrophage clearance. Adverse health effects result when the clearance capacity via macrophage, chemical, and physical mechanisms, is exceeded by particle deposition rates. As with asbestos fibers (Snipes, 1995), small particles may be transported within phagocytic cells into the lymph system, and may also be able to penetrate the circulatory system, where they can then be transported to other organs and deposited. The fact that commonly nonfibrous crystalline silica can be pathogenic under high-dose exposures indicates that particle shape is not the sole factor in pathogenicity.

9.07.8.3.2 Particle solubility and dissolution rates

The rates at which inhaled particles dissolve *in vivo* are thought to play important roles in their biopersistence, and therefore their ability to trigger fibrosis, cancer, and other diseases. Dissolution rates are a complex function of the chemical solubility of particles in the body fluids, coupled with factors (such as crystal structure and mineral surface properties) that determine the rate at which particles dissolve. For example, several lines of evidence indicate that the amphibole asbestos minerals and erionite are less readily dissolved in lung, interstitial, and phagolysosomal fluids than chrysotile asbestos. This enables their fibers to persist for longer periods of time in the lungs and adjacent tissues, thereby imparting a greater potential to trigger fibrosis and cancer (Sébastien *et al.*, 1989; Churg *et al.*, 1993, 1989; Johnson and Mossman, 2001).

A variety of studies have used *in vitro* biodurability tests to the determine dissolution rate of various silicate minerals in simulated lung and lysosomal fluids (Hume and Rimstidt, 1992; van Oss *et al.*, 1999; Jurinski and Rimstidt, 2001; Werner *et al.*, 1995). Most *in vitro* studies of mineral solubility analyze changes over time in solution chemistry for a limited number of constituents such as aqueous silica, magnesium, and iron. With this information, coupled with analytical data on the composition of the fibers after being leached, dissolution rates can be

inferred based on the total amount of these constituents released over time, and dissolution processes can be inferred based on element ratios in the leach fluid and the characteristics of the leached fibers. These studies have shown that the dissolution rate of chrysotile is quite high in SLFs, and are higher than for the amphibole asbestos minerals, erionite, talc, and quartz. A variety of studies have found that magnesium is preferentially leached from the surfaces of talc particles, chrysotile fibers, and crocidolite fibers, leaving behind a rind of leached material enriched in silica. Werner *et al.* (1995) also found that iron was leached preferentially from crocidolite in the presence of organic iron chelators. It has been proposed that this chemical leaching process weakens the fibers, thereby making them more susceptible to breakage and therefore less biopersistent. On the basis of these results, Jurinski and Rimstidt (2001) proposed that silica release from particle surfaces is the rate-limiting step in their dissolution.

9.07.8.3.3 Particle solubility: insights from chemical modeling calculations

Hume and Rimstidt (1992) used thermodynamic constraints to show that lung fluids should be substantially undersaturated with respect to chrysotile. Taunton *et al.* (2002) and Gunter and Wood (2000) used a thermodynamic phase diagram approach to model potential chemical reactions between asbestos and simplified lung fluids that might alter the asbestos to other minerals *in vivo*; their model results suggested that silica, and possibly talc, are predicted to precipitate as chrysotile dissolves; the precipitation of silica is consistent with the silica-rich leached rind produced by the *in vitro* solubility studies discussed above.

We have used chemical speciation calculations to predict the relative saturation indices of quartz and of different asbestos-forming minerals in equilibrium with solutions having inorganic electrolyte concentrations (Table 4) approximating those of interstitial fluids (approximating lung fluids), intracellular fluids, and inferred lysosomal fluids (Figure 9). The results illustrate both the challenges and benefits of applying chemical speciation calculations to understand mineral solubility in bioinorganic systems. For example, a large number of minerals are predicted to be quite highly supersaturated in the interstitial fluids, including hydroxyapatite, a key mineral component of bones (Skinner, 2000), and other minerals (such as calcite) that should from a kinetic standpoint, be able to precipitate *in vivo*. This suggests that the calculations may have used fluid compositions that were too simple (i.e., neglecting the organic acids and their calcium complexes may overestimate carbonate and hydroxyapatite saturation), or incorrect (i.e., perhaps aluminum concentrations are too high, and published phosphate concentrations may not differentiate inorganic from organic phosphate). Also, it may not be appropriate to extrapolate our knowledge of mineral precipitation kinetics in inorganic systems to conditions *in vivo*. However, even with these potential shortcomings, the simple speciation calculations depicted in Figure 9 do provide some potentially useful information. For example, quartz is calculated to be slightly supersaturated in both the interstitial and intracellular fluids, and several of its polymorphs, including chalcedony, are slightly undersaturated. This indicates that there may not be a strong thermodynamic driver for quartz dissolution *in vivo*, and helps explain the development of silica-rich rinds on dissolving silicate particles (Jurinski and Rimstidt, 2001) as in chrysotile dissolution:

$$\begin{aligned} &Mg_6(Si_4O_{10})(OH)_8 + 12H^+ \\ &\quad \Rightarrow 6Mg^{2+} + 4SiO_{2\ aq} + 10H_2O4SiO_{2\ aq} \\ &\quad \Rightarrow 4SiO_{2\ Quartz} \end{aligned}$$

However, dissolution studies indicate that quartz does dissolve, albeit slowly, *in vitro* (Jurinski and Rimstidt, 2001); this suggests that organic species or some other ligand not considered in these calculations may be helping to complex aqueous silica and therefore driving the dissolution. Further work is needed to evaluate the potential role of organic complexes with silica *in vivo*.

The various asbestos-forming minerals are predicted by the speciation calculations (Figure 9) to be moderately undersaturated in the pH 7.4 interstitial fluids and extremely undersaturated in the acidic lysosomal fluid compositions, and therefore should have a substantial tendency to dissolve. The amphiboles are predicted to be substantially more soluble than chrysotile, and so should have a greater tendency to dissolve than chrysotile, contrary to the observed relative dissolution rates. This provides support for the conclusion by Hume and Rimstidt (1992), and Jurinski and Rimstidt (2001) that kinetic factors play important roles in determining particle dissolution rates. Although erionite was not considered in the calculations, several sodic zeolites such as stilbite were considered. They are only slightly undersaturated in the lung fluid proxy at pH 7.4, suggesting that the biodurability of erionite may be due in part to its low solubility in the lung fluids.

The various asbestos-forming minerals (and silicates in general) are predicted by the speciation calculations (Figure 9) to become supersaturated

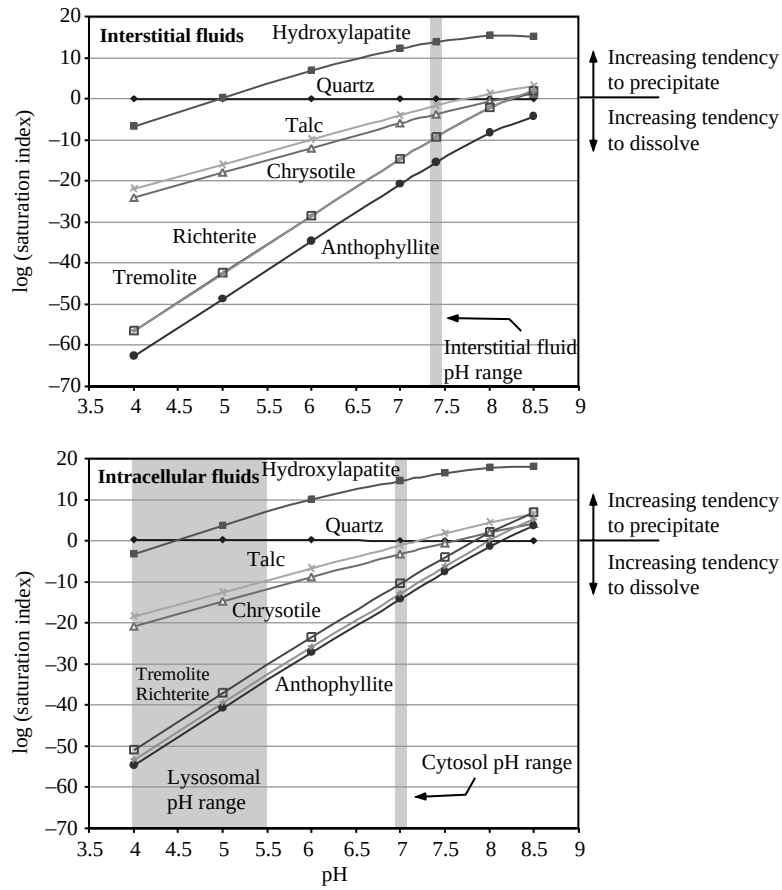

Figure 9 Plots showing the calculated mineral saturation indices as a function of pH for hydroxylapatite, quartz, and various asbestos-forming minerals in electrolyte solutions approximating the electrolyte compositions of lung fluids (approximated by interstitial fluids, upper plot) and intracellular fluids (lower plot). Electrolyte concentrations used as input were taken from Table 4. The CO_2 partial pressure was fixed at the value for venous plasma for each speciation at a different pH. Organic species such as amino acids and other organic acids were not included in the calculations, but likely would have the effect of decreasing the calculated saturation indices somewhat due to their complexation with cations.

in the interstitial fluids with shifts to higher pH (to near 8–8.5). Alkaline, reactive particles that are inhaled with the asbestos fibers, could increase the pH of the lung fluids. The solubility drivers for fiber dissolution might then be diminished. Silicate fiber dissolution should also consume acid according to the previous dissolution reaction for chrysotile, and the following dissolution reaction for tremolite:

$$Ca_2Mg_5(Si_8O_{22})(OH)_2 + 14H^+ \Rightarrow 2Ca^{2+} + 5Mg^{2+} + 8SiO_{2\ aq} + 8H_2O$$

It is interesting to speculate whether, in spite of the lung's attempts to produce more fluids at the site of foreign particle deposition, fiber dissolution could increase the pH of the local lung fluids so that they sufficiently become saturated with fibrous silicates, thereby limiting further dissolution.

9.07.8.3.4 Mitigating or exacerbating effects of trace elements and accessory minerals

Most toxicological studies focus on the toxicity or solubility behavior of a particular sample of a given mineral such as chrysotile, tremolite, or talc. They do not tend to examine the role that variations in morphology, trace element content, accessory minerals, and other characteristics between the same mineral from different samples in the same geologic locality, and between samples from different geologic localities, can play in *in* vitro and *in vivo* biodurability, and therefore toxicity. These parameters have been demonstrated to play important roles in the rate at which other minerals, such as sulfides, weather under environmental conditions (see summary in Plumlee, 1999), and so are also likely to be important for particle durability *in vivo*.

Hochella (1993) cites several studies, such as Nolan *et al.* (1991), in which the same mineral from different localities shows a variable range of carcinogenicity in laboratory animals. Johnson and Mossman (2001) summarize results of some studies that have found that the fiber length and biological activity can vary substantially between different chrysotile samples collected from different geological localities.

Ziegler *et al.* (2002) have systematically characterized and compared 5 sets of asbestos toxicological standards (5 amosites, 4 anthophyllites, 6 chrysotiles, 5 crocidolites, 4 tremolites). Substantial variability was found in a number of mineralogical parameters between different standards of the same asbestos minerals, such as: morphology (i.e., length, width, "curlyness," etc.), the types and abundances of accessory or contaminant minerals present with the fibers, and the major and trace element compositions. For example, a number of the toxicological standards contain accessory minerals such as quartz and others that, although present in generally low to moderate amounts, are themselves potentially toxic. In addition, a variety of heavy metals are present, some in readily leachable form, including redox-active and/or potentially toxic metals such as chromium and nickel. All of these additional characteristics could serve to confound the interpretation of toxicological studies. In fact, *in vitro* 24-hour biodurability and cell line toxicology tests of the different standards also produced highly variable results (Ziegler *et al.*, 2002). Although further work is needed (such as longer-term biodurability and *in vivo* toxicology tests on all the standards), our results to date confirm the results of previous studies that mineralogical and geochemical variations between samples of a given asbestos mineral may have important effects on their relative biodurability and toxicity.

Some accessory minerals that accompany the inhaled dose of particles may themselves be reactive (such as pyrite, an iron sulfide) and may be able to modify fluid chemistry sufficiently to enhance or diminish particle solubility, or to release redox-active species such as iron. For example, the well-documented decrease in crystalline silica toxicity when combined with other, nonsilica mineral particles (SSDC, 1988) implies that the other mineral particles are reacting chemically with the body fluids and the silica to modify the surface chemistry of the silica that induces ROS generation and cytotoxicity.

9.07.8.3.5 Particle crystal structure

Jurinski and Rimstidt (2001) concluded that particle dissolution rates are more strongly influenced by crystal structure than by bulk chemistry, citing the greater rates of chrysotile dissolution compared to those of talc *in vitro*. They concluded that chrysotile asbestos fibers dissolve more readily than talc, because their rather unique crystal structure (the fibers are constructed of sheets coiled around the fiber axis) allows material to be readily leached from layers as they unwrap along the entire fiber length, rather than just from the grain edges, as in the case of talc. This may also help to explain the greater dissolution rate of chrysotile asbestos fibers than amphibole asbestos fibers (which form by the separation of coarser crystals along irregular planes parallel to the long crystal axis; Ahn and Buseck (1991)), even though the body fluids are predicted to be more undersaturated with respect to the amphiboles than to chrysotile (Figure 9). Hochella (1993) and Crawford (1980) have also shown that mineral dissolution can occur preferentially along crystal structural defects.

9.07.8.3.6 Particle surface features

Additional features that have been cited as potential contributors to fiber pathogenicity include a variety of surface features such as surface- and near-surface composition; surface area, surface morphology (microtopography) and atomic structure, surface charge (coupled with its dependence on the pH and chemical composition of the surrounding fluids), and relative hydrophobicity versus hydrophilicity (Hochella, 1993; Guthrie, 1997; van Oss *et al.*, 1999; Johnson and Mossman, 2001; Giese and van Oss, 1993). The net surface charge of a particle can be either negative or positive, and may influence chemical interactions with surrounding fluids and tissues; however, van Oss *et al.* (1999) found no systematic correlation between surface charge and particle mineralogy. Although hydrophobic minerals can sorb biopolymers more strongly than hydrophilic minerals, and hydrophobic particles are more readily phagocytized than hydrophilic particles, van Oss *et al.* (1999) found no consistent correlation between particle hydrophobicity, hydrophilicity, and potential pathogenicity.

9.07.8.3.7 Fluid–mineral reactions that generate free radicals

A number of studies have proposed that chemical interactions between mineral particles and body fluids can lead to the production of free radicals and other ROS, which can in turn potentially trigger cell injury such as lipid peroxidation, DNA damage, and ultimately cell mutation and carcinogenesis (Hardy and Aust, 1995; Kamp *et al.*, 1992; Lund and Aust, 1992;

Aust and Lund, 1990; Werner *et al.*, 1995; Graham *et al.*, 1999; Shi *et al.*, 2001).

Much attention has focused on the potential for ferric iron released from asbestos fibers to react with organic reductants in the body fluids and subsequently to generate free radicals and ROS. Werner *et al.* (1995) used *in vitro* leach tests to show that organic chelators can effectively leach ferric iron from crocidolite fiber surfaces over prolonged periods of time. Lund and Aust (1992) used *in vitro* tests with crocidolite to show that increased mobilization of ferric iron from crocidolite surfaces correlated well with increased production of DNA strand breaks. Graham *et al.* (1999) concluded that grinding of iron-containing amosite fibers led to a decrease in the amount of ferric iron that could be leached from the fiber surface, thereby indicating another potential cause for long fibers to be more pathogenic than short fibers. In contrast to these studies, van Oss *et al.* (1999) were not convinced that asbestos iron content is an important factor in asbestos pathogenicity. They cited as an example the high pathogenicity of erionite, which is a sodium-rich zeolite that generally has a very low iron content. However, Hardy and Aust (1995) pointed out that the release of iron sorbed on erionite surfaces can trigger a short-term increase in DNA breaks. Werner *et al.* (1995) cited the low iron content of erionite to underscore the fact that the iron content of fibers is probably only one of several potential triggers for fiber pathogenicity.

Freshly ground particles of crystalline silica can develop surface Si—O bonds and other surface features that, when reacted a with oxygenated water-rich fluid can foster the generation of ROS (Shi *et al.*, 2001). Si—OH groups can form on the surface of silica particles as reactions with water hydrate surface Si—O bonds; the Si—OH groups are also tied to the formation of ROS. With increasing time after grinding, the generation of ROS diminishes. Such an effect may also occur with other silicates such as asbestos.

Mineral particles likely also indirectly trigger production of free radicals as a result of phagocyte activation and cytokine release (Kamp *et al.*, 1992; NIOSH, 2002).

9.07.8.3.8 Smoking—a confounding factor

Smoking is a well-known trigger of respiratory diseases such as emphysema and lung cancer. Workers who smoke and who are exposed to excessive levels of particulates such as silica or asbestos have a combined lung cancer risk that is greater than for smoking or particle exposure alone (Holland and Smith, 2001). As a result, smoking (and exposure to other environmental pollutants) can make it difficult, but not impossible, to interpret epidemiological data for silica- or asbestos-related disease.

9.07.8.3.9 Dose—a key factor

Based on a number of indications from the literature discussed above, it is clear that the dose (intensity and/or duration) of inhalation exposure to insoluble, sparingly soluble, and slowly dissolving particles is a key factor in particle pathogenesis. Particle composition, morphology, biodurability, surface effects, and other characteristics may influence the intensity and the duration threshold above which disease is triggered. For example, equant biodurable particles such as silica can cause disease, but the intensity and duration of exposure required are probably greater than for fibrous particles that are less easily cleared by the macrophages. Among fibrous particles, lower doses are seemingly required for those that are less readily dissolved, have key toxic elements such as iron, and have morphologies that enhance their ability to pierce and migrate into tissues. Clearly, a profitable area of future research will be the continued examination of the link between toxicity and dose *as a function of particle characteristics*.

9.07.9 THE MEDICAL GEOCHEMISTRY OF EARTH MATERIALS WITH READILY SOLUBLE, BIOACCESSIBLE, AND/OR BIOREACTIVE COMPONENTS

Most earth materials to which humans can be exposed are likely to contain a complex mixture of different minerals or materials, which may differ substantially in their relative biosolubility and bioreactivity, as well as the bioaccessibility and chemical form of potential toxins that they contain. In the following discussion, we will discuss various earth materials as examples of the role that mineralogy, chemical composition, and geochemical properties of complex materials can play in their bioaccessibility, biosolubility, bioreactivity, and therefore potential toxicity.

9.07.9.1 Mining Wastes, Tailings, Smelting By-products

A primary human health concern associated with mine wastes, tailings, and smelting by-products produced during the extraction of metals from metallic mineral deposits has been the incidental ingestion exposure, and resulting heavy metal uptake, especially for small children who play on waste piles, tailings, slag heaps, or

soils containing or affected by these wastes or smelter emissions (Ruby *et al.*, 1993, 1996). There has also been some recognition for potential metal uptake via the inhalation of windblown particulates derived from mine wastes (Mullins and Norman, 1994). Silicosis has long been recognized as a potential health concern for miners (Daroowalla, 2001; NIOSH, 2002), especially in the past, when dust-control measures were not practiced during mining; however, it is not noted as a potential health concern resulting from environmental exposure to windblown dust from mine and processing wastes.

9.07.9.1.1 Mineralogy

Mine wastes are composed of unmineralized or mineralized, but low-grade, rock material that must be removed in order to mine high-grade mineralization. The material can range in size from coarse boulders to micrometer-size particles. Tailings are composed of mineralized material that has been ground to sand size or smaller, and from which most of the minerals of economic interest (such as gold, or sulfides of copper, lead, zinc, mercury, etc.) have been removed. Sulfide ore smelting results in the formation of waste slag and gaseous emissions containing both sulfur dioxide and particulates with high concentrations of the metals contained in the ores.

Mine wastes, tailings, and smelter slag and emissions can contain complex mixtures of minerals that are typically a predictable function of the geologic characteristics of the deposit type being mined, coupled with the ambient climate/environmental characteristics and the mining or mineral processing method used. See Chapter 9.05 and Plumlee (1999) for a detailed discussion.

Minerals present in mine wastes and tailings include:

- Primary minerals formed in the ore deposit prior to weathering and erosion, including a wide variety of metal sulfides and sulfosalts, metal oxides, metal- and alkaline-earth carbonates, sulfates, crystalline silica, clays, and other silicates. Many metal sulfides (especially iron sulfides such as pyrite), when exposed by erosion or mining to atmospheric oxygen and water, can form acid–rock drainage (ARD).
- Secondary metal oxides, carbonates, sulfates, and phosphates formed by weathering of the ore deposit prior to mining.
- Soluble metal sulfate salts formed by the evaporation of ARD.
- Iron and aluminum oxyhydroxides and hydroxysulfates with sorbed metals that form in ARD and in surface waters affected by ARD.

Smelter slag is typically composed primarily of an amorphous, silica- and calcium-rich material formed by the reactions of iron in the ores with silica and lime used as flux (Ruby *et al.*, 1996; Davis *et al.*, 1992, 1996; Plumlee, 1999). The slag also commonly contains remnant sulfides from ore that was not completely smelted, and a variety of oxides, silicates, chlorides, sulfates, and other minerals containing the metals originally present in the ores. Airborne particulates generated by smelting are a complex mixture of fine-grained (<100 μm) metal oxides, silica-rich phases, and sulfates.

Soils that have been contaminated by mine wastes, tailings, smelter slags, or smelter particulates can contain a complex mixture of: minerals present in the soils prior to contamination; minerals contributed by the contaminants; minerals formed by soil weathering, biological reactions, and chemical reactions with infiltrating waters and soil moisture; windblown dust, and other anthropogenic materials (Ruby *et al.*, 1999). For example, reactions of lead oxide with soil moisture in alkaline soils can precipitate lead carbonate, whereas reactions in acidic soils can precipitate lead sulfate.

Hence, mine wastes, tailings, and smelting by-products can contain a wide variety of minerals, including minerals that are bioreactive (such as acid-generating sulfides and evaporative sulfate salts), minerals that contain potentially bioaccessible heavy metals and metalloids (lead, cadmium, arsenic, mercury, zinc, copper, nickel, uranium, molybdenum, antimony, etc.), and minerals that are biodurable (such as quartz and, in some deposit types, asbestiform silicates).

9.07.9.1.2 Ingestion bioaccessibility

As summarized by Ruby *et al.* (1999), a variety of mineralogical characteristics control the oral bioaccessibility of metals such as lead and arsenic (Figure 10), including: the types and grain sizes of the minerals in which they occur, and their degree of encapsulation by other, less reactive or soluble minerals. In addition, based on observations made for the weathering of mine wastes (Plumlee, 1999), the reactivity (and hence bioaccessibility) of sulfides and other mineral groups can be strongly influenced by their crystal morphology (fibrous, framboidal, botryoidal, massive, blocky), and the concentrations and types of trace elements in their crystal structure.

Results of various *in vitro* and *in vivo* bioaccessibility studies (Ruby *et al.*, 1993, 1996, 1999; Davis *et al.*, 1992, 1996, 1993; Borch *et al.*, 1994; Dieter *et al.*, 1993) indicate that some aspects of the fate of metals or metalloids leached from mine wastes that enter the gastrointestinal system can be readily understood based on their mineralogical characteristics, coupled with a knowledge of how

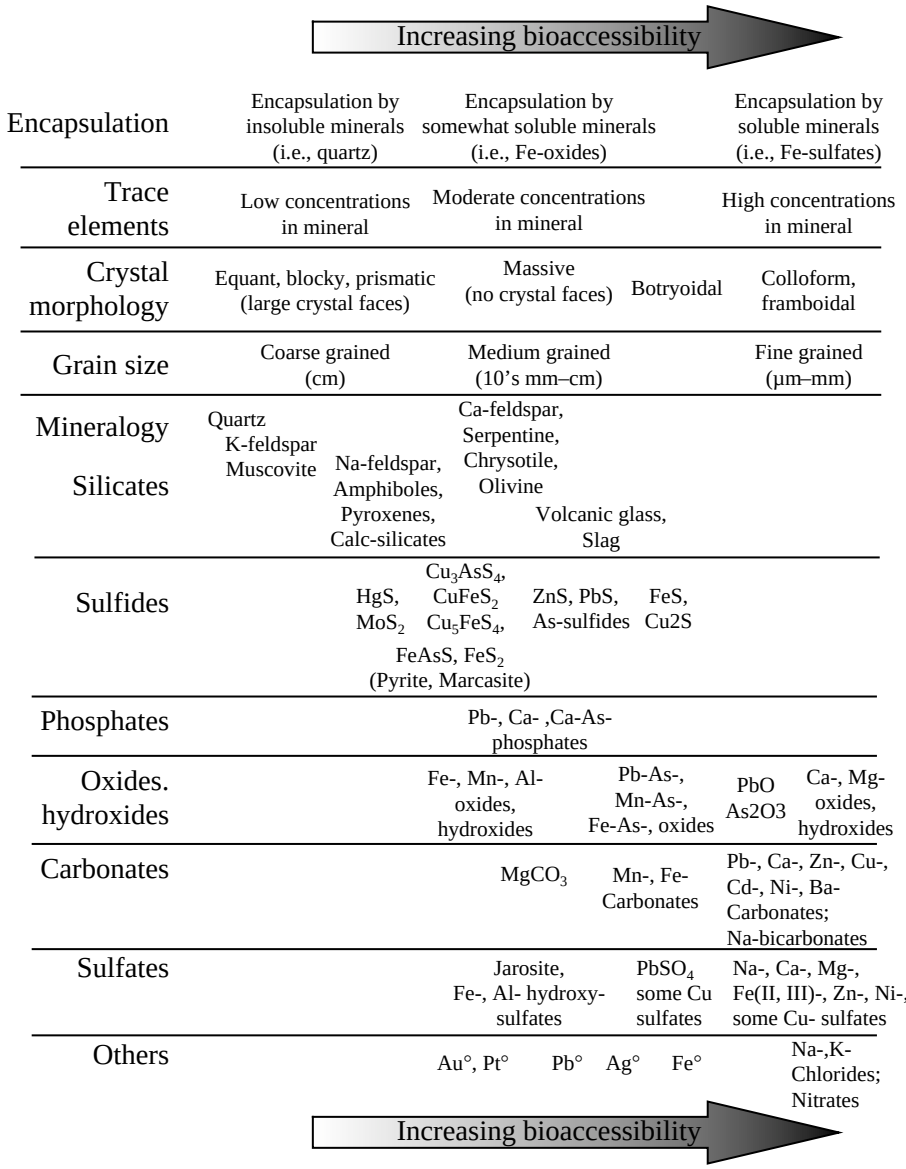

Figure 10 Influence of mineral type, crystal morphology, grain size, degree of encapsulation, and trace element content on bioaccessibility. Differences in bioaccessibility between different mineral types should be considered as qualitative, and may vary depending upon the chemistry of the surrounding fluids. For example, sulfides are all substantially much more bioaccessible under oxidizing conditions than reducing conditions. Similarly, carbonates are much more bioaccessible under acidic than alkaline conditions (sources Ruby *et al.*, 1999; Plumlee, 1999; Nordstrom and Alpers, 1999).

the metals or metalloids might respond (Smith and Huyck, 1999) to the redox, pH, and fluid compositions of the stomach and intestines. Although sulfides are likely to be highly undersaturated in the gastric fluids, particles broken from coarse sulfides should not dissolve substantially during the hour-scale residence in the stomach. Similarly, acid-stable, relatively insoluble sulfates and phosphates (such as jarosite, alunite, plumbojarosite, and others) should not dissolve appreciably while in the stomach. The most soluble, reactive carbonates may dissolve partly to completely, as may some fine-grained metal oxides. The fine-grained sulfides that weather most rapidly (especially those that have high trace element contents), as well as readily soluble metal sulfate and metal chloride salts, have the highest potential for the release of their contained metals into the stomach fluids. In the acidic conditions of the stomach, most base metals such as lead, iron, copper, zinc, cadmium, nickel, and cobalt are likely to be complexed primarily by chloride, less so by organic acids due to their degree of protonation. Elements such as arsenic, antimony,

and molybdenum are likely to be present as oxyanion species, and so their concentration may not be enhanced by the complexing agents in the stomach. The redox response of species having varying redox state is uncertain, but may be quite variable in the stomach depending on the redox kinetics of the species, along with the redox kinetics of the multiple redox couples (such as dissolved oxygen or various organic couples) potentially active in the stomach fluids. For example, it is likely that aqueous ferrous iron liberated by pyrite oxidation will not be oxidized to ferric iron in the stomach by reaction with dissolved oxygen (if any has been introduced by swallowing); however, it is unclear to what extent ferric iron and other oxidized species (such as sulfate, arsenate, etc.) that are released from soluble salts may be reduced by reaction with organic compounds in the stomach fluids.

Once they have reached higher pH, reducing conditions of the intestinal tract (Davis *et al.*, 1992), sulfides should be more stable, and may actually precipitate if reduced sulfur is present. Other solids, such as hydroxides or hydroxysulfates of aluminum, and possibly iron, may also precipitate. The increased pH should also lead to the increased sorption onto particulates of various metals and metalloids such as lead and copper (Smith, 1999). However, *in vitro* tests (Ruby *et al.*, 1993) indicate that the increased complexing with unprotonated organic acids and enzymes helps offset the pH-driven precipitation and sorption of the base metals that were dominantly chloride-complexed in the stomach fluids. Arsenic and other oxyanionic species are likely to be sorbed as the stomach acids are neutralized, but may be partially desorbed once higher pH values are reached in the intestine (Ruby *et al.*, 1996).

9.07.9.1.3 Respiratory bioaccessibility

Only limited work has been done on the bioaccessibility of metals in windborne mine waste and tailings material, and so much must be inferred. Mullins and Norman (1994) analyzed the size distribution, metal content, and metal extraction by simulated biofluids (lung, gastric, intestinal) of surface materials (soils) collected from several mine waste piles in the Butte, Montana, district. They found that the concentrations of arsenic, cadmium, copper, manganese, and lead were commonly greatest in the smallest size fractions ($<4.7\ \mu m$) of the waste dump material. The percentage of metals leached from the fine fraction was quite variable, but not in any consistent way, between different metals, different dumps, and different extraction fluids. The variability between metals extracted, dumps, and fluids results primarily from mineralogical variability within and between the dumps; however, the mineralogical characteristics of the dump materials were apparently not determined.

As with ingestion exposures, the geochemical aspects of inhalation exposures to mine waste and tailings particles are likely to be influenced strongly by the mineralogical characteristics in Figure 10. However, many aspects of the particle dissolution reactions and redox reactions are still quite speculative. Because the lung and macrophage fluids are likely to have Eh values favoring aqueous sulfate over sulfide (Figure 5), it is quite possible that particles broken from coarse, well-crystallized sulfides react and dissolve relatively slowly in the lung fluids and the macrophage lysosomal fluids, and may be somewhat biodurable. They might also serve as a long-term source of acid and metals that slowly leach into the surrounding fluids and tissues, possibly triggering inflammation or, in the case of variable oxidation state elements such as iron or arsenic, trigger production of free radicals and DNA breakage. Particles of fine-grained or trace-element-rich sulfides might be expected to dissolve more rapidly, possibly producing higher levels of acid and metals in their surroundings over a shorter period of time following exposure. The soluble metal sulfate salts probably dissolve quite quickly in the lungs, producing high levels of acid and metals over a relatively short period following exposure, as has been shown for coal dusts containing abundant pyrite and oxidation products such as ferrous sulfate (Huang *et al.*, 1993).

It is possible that a variety of secondary phases may precipitate in the lungs or in the macrophages, or may form reaction rinds on sulfide particles, as the result of sulfide oxidation or soluble salt dissolution *in vivo*. For example, phosphate (present in high concentrations in both the lung and macrophage fluids) may combine with calcium, aluminum, iron, lead, or other metals released from the salts to precipitate a variety of less soluble phosphate phases. Other secondary phases might include hydroxides or hydroxysulfates of aluminum or iron, or sulfates such as gypsum.

Because it is unclear which of many possible redox couples are active in the lung or macrophage fluids, it also is unclear what might happen to redox-sensitive species such as iron, arsenic, or manganese released from the sulfides and salts into the lungs or alveolar macrophages. Although dissolved oxygen concentrations in the lung fluids are likely high, and so might tend to shift reduced species to their oxidized forms, it is unclear whether organic ligands in the lung fluids could either inhibit this oxidation, and/or possibly shift oxidized species toward their reduced forms.

9.07.9.2 Coal and Coal Fly Ash

Coal is the collective term that refers to organic-rich sedimentary rock materials formed by the fossilization of plant matter. Coal can have different ranks, depending on the temperature and pressure to which the organic matter has been subjected following deposition. Anthracite has the highest rank and the highest carbon content (95%); progressively lower ranks of coal have a progressively lower carbon content. Coal can also have variable amounts of accessory materials interspersed with the organic components, including a variety of clays, carbonate minerals, crystalline silica or other silicate minerals (collectively termed ash), and iron sulfides such as pyrite and marcasite. In addition, coals can contain very high levels of a variety of potentially toxic metals and metalloids such as mercury, cadmium, and arsenic.

The primary health problems tied to coal are coal workers' pneumoconiosis (CWP, also called black lung disease), progressive massive fibrosis, silicosis, chronic bronchitis, and emphysema, which result from the prolonged inhalation exposure to coal dusts generated during mining or coal processing (Daroowalla, 2001; Castranova, 2000; Castranova and Vallyathan, 2000). These health effects have traditionally been thought to result from the biodurability of the organic-rich coal dusts (and accessory silica dusts) in the lungs, the resulting cytotoxicity of the particles, and the activation of macrophages with their production of oxidants and ROS (Castranova, 2000). Huang *et al.* (1998) proposed that the potential of a particular coal to generate CWP increases with increasing content of acid-soluble ferrous iron and with the decreasing acid-buffering capacity of coal (presumably reflecting decreasing carbonate mineral content). They proposed that the release of acid soluble iron is enhanced in coals with lower acid-buffering capacity, and that the release of ferrous iron and its subsequent oxidation in the pulmonary environment leads to oxidative stress, formation of free radicals, and resulting lung injury. In an earlier paper, Huang *et al.* (1993) proposed that ferrous iron is released during the solution of ferrous sulfates (such as melanterite) that formed as an oxidation product of pyrite under acidic conditions prior to inhalation; under alkaline conditions (e.g., if carbonates are present), pyrite oxidation would lead to the rapid oxidation of ferrous to ferric iron and preclude the buildup of ferrous sulfate on the oxidizing pyrite, thereby diminishing the potential for ferrous iron release in the pulmonary environment. It is possible, however, that the oxidation of sulfide particles themselves in the lungs could generate acid and release ferrous iron (and other potentially toxic elements) into the surrounding fluids and tissues.

Coal fly ash (CFA) is the particulate material, typically characterized by the presence of many silt- to clay-sized particles, which is produced by the combustion of ground coal (Jones, 1995). The particles are composed of quartz, mullite (an aluminum silicate), iron oxides, aluminosilicate glasses, and gypsum. SO_2 and a wide variety of trace elements can be sorbed on the particle surfaces. Depending on the proportions of carbonates to iron sulfides in the coal prior to combustion, CFA can generate highly alkaline (high carbonate/sulfide coal) to somewhat acidic (low carbonate/sulfide coal) water leach solutions. The types and concentrations of metals and metalloids released from CFA into water leach solutions depend on their initial concentration in the coal and on the alkalinity or acidity of the CFA. In general, metals such as cadmium, copper, manganese, iron, nickel, lead, and zinc are released in greatest quantities from acidic CFA, whereas elements that form oxyanionic species such as arsenic, boron, molybdenum, selenium, antimony, and vanadium are released in greatest quantities from alkaline CFA.

A variety of *in vitro* and *in vivo* toxicological studies have examined the potential health effects of CFA. Most of these studies have concluded that iron release from CFA can generate free radicals, and therefore can trigger DNA damage and toxicity (Smith *et al.*, 1998, 2000; Veranth *et al.*, 2000; van Maanen *et al.*, 1999; Chen *et al.*, 1990). Hence, the deleterious effects from inhalation exposure to CFA may be linked to its content of leachable iron, its alkali content, and the amounts of soluble salts that can dissolve to generate acid and thereby enhance iron release. However, the chemical reactions between CFA and lung and macrophage fluids, and the potential health effects of leachable metals and metalloids other than iron must be studied further.

9.07.9.3 Volcanic Ash, Gases, and Vog

Volcanic ash (VA) is composed of a mixture of pumice, glass shards, rock fragments, and variable proportions of crystals or crystal fragments of various silicate minerals such as (depending upon the composition of the magma being erupted) pyroxenes, feldspars, quartz, and cristobalite. In addition, small amounts of minerals such as clays may be present due to alteration of the silicates by acidic aerosols and gases. VA that is freshly erupted can have a wide variety of trace metals that are present in soluble halide salts or that are loosely sorbed onto particle surfaces; these metals and salts result from interactions with air of ash particles and the gaseous components

(including acidic gases) of the volcanic plume (Smith *et al.*, 1982, 1983).

Health concerns regarding VA have focused primarily on respiratory effects in heavily exposed populations such as short-term respiratory irritation and longer-term development of pneumoconiosis. The potential toxicity of crystalline silica in the ash has been of particular concern (Baxter *et al.*, 1999; Wilson *et al.*, 2000; CDC, 1986; Vallyathan *et al.*, 1983a,b; Baxter *et al.*, 1983). These studies indicate that the potential toxicity of VA can vary between different ash eruptions from a given volcano and between different volcanoes. The variability is probably due to difference in the crystalline silica content and in the proportion of respirable particles.

Relatively little attention has focused on the potential health effects of metal release from respired ash. Chemical leach tests using water, dilute HCl, and carbonate–bicarbonate solutions of ash from Mount St. Helens (Smith *et al.*, 1983; Hinkley, 1987) and other active volcanoes (Smith *et al.*, 1982) have shown that a wide variety of cations, metals, and anions are readily leached from fresh ash, including, depending upon the volcano: Ca, Cl, SiO_2, SO_4, Mg, Na, Fe, Mn, in 1–100 mg L^{-1} concentrations (1 : 4 solid : liquid by weight); and Zn, Cd, and Pb in $\mu g\, L^{-1}$ concentrations. It is unclear whether sufficiently high concentrations of metals such as iron and manganese could be released from ash *in vivo* over either the short term or the long term to trigger free radical generation and DNA damage. Recent studies of ash from the Soufrière Hills volcano have found high surface reactivity and high levels of hydroxy radicals that were attributed to release of ferrous iron from the ash (Horwell *et al.*, in press).

Volcanic smog (known as vog) is a mixture of atmospheric gases and suspended liquid and solid particles. It forms by the reaction of sulfur dioxide and other volcanic gases with atmospheric moisture, gases, dust, and sunlight (Sutton *et al.*, 1997). Vog consists primarily of sulfuric acid and other sulfate compounds, and can contain a variety of heavy metals, including selenium, mercury, and arsenic (Sutton *et al.*, 1997). Laze, a volcanic haze, forms when molten lava flows into the sea and vaporizes seawater (Sutton *et al.*, 1997). It has many of the same characteristics as vog, with the exception that it probably contains higher levels of chloride and hydrochloric acid derived from seawater.

Adverse health effects that have been noted as the result of vog produced by active Hawaiian volcanoes include acid-triggered irritation of the mucous membranes (eyes, nose, and throat), increased asthma, respiratory distress, increased susceptibility to respiratory ailments, headaches, watery eyes, and lack of energy (Sutton *et al.*, 1997). These problems increased on the island of Hawaii during the eruption cycle of Kilauea volcano that began in 1986. Increased lead uptake by local residents has also been noted. This is thought to originate from water collected on roofs for domestic consumption, because vog-generated acid rain leaches lead from metal roofing, flashing, etc.

The respiratory health effects of vog and volcanic gases such as sulfur dioxide are tied to the generation of locally acidic environments in the lung and respiratory tract fluids by condensation of SO_2 and other acid gases, uptake of acid-sulfate aerosol droplets, and the dissolution of acid-bearing, sulfate- or chloride-rich salts from the vog particulates by the fluids lining the respiratory tract.

9.07.9.4 Dust from Owens Lake, California, and Other Dry Lake Beds

In its natural condition, Owens Lake was the terminal lake of the Owens River, which drains much of the eastern slope of the Sierra Nevada in central California. However, in the early 1900s, water withdrawal for municipal consumption in Los Angeles caused the lake to dry up, leaving behind a dry lake bed whose sediments have become the biggest single point source of dust in the United States (Raloff, 2001); during the passage of storm systems, the 24 h average concentrations of PM10 dust particles (those less than 10 μm in diameter) can exceed 150 $\mu g\, m^{-3}$, more than 10 times the maximum amount allowed under Federal air quality regulations. More recent studies indicate that Owens Lake dust is transported as far as 400 km to the east (Reheis *et al.*, 2002).

The Owens Lake dusts are derived from lake bed sediments containing abundant alkaline evaporative salts of sodium, chloride, carbonate/bicarbonate, and sulfate, including, e.g., halite, natron, thermonatrite, mirabilitie, and trona (Saint Amand *et al.*, 1986). In addition, the dusts contain a variety of silicates and other minerals derived from local alluvial material, and possibly some mine waste materials from the Cerro Gordo lead–zinc–silver mining district on the east end of Owens Lake.

Chemical analysis (Reheis *et al.*, 2002) of the <50 μm fraction of the dusts that originate from the dry Owens Lake bed indicate that they contain quite high levels of a variety of metals or metalloids including: iron (several percent); zinc (tens of thousands of ppm), manganese and lead (hundreds of ppm); arsenic, chromium, nickel, and lithium (tens of ppm), and uranium (several ppm). Given the oxidized conditions of the playa lake surface, it is likely that arsenic, chromium, and

other redox-sensitive elements are present in their oxidized forms.

The Owens Lake dusts have been recognized as a potential human health hazard. Remediation efforts have recently been implemented to help mitigate dust generation from the dry lake beds. However, we are not aware of any systematic epidemiological or exposure studies that have been carried out to assess or document the health effects on people living near Owens Lake.

Chemical leach tests of the <50 μm size fraction of dust samples collected around Owens Lake, using water (Reheis *et al.*, 2001, and our unpublished data) and SLFs (our unpublished data), show that the dusts are sufficiently alkaline and reactive to shift the pH of water and SLF to values near 10.5 and 9.5, respectively. Arsenic, chromium, vanadium, molybdenum, lithium, zinc, and other trace metals or metalloids are readily solubilized from the dusts. The trace metals or metalloids leached in the greatest quantities are those that form oxyanion species or abundant carbonate complexes in solution, and that are therefore mobilized most effectively under the alkaline conditions generated by the alkaline dusts.

These results suggest that evaporative playa lake sediments and dusts generated from dry lake beds can be potentially significant sources of reactive, alkaline material with high levels of soluble, potentially toxic trace metals and metalloids. Further studies are needed to determine whether such dusts pose a substantial health hazard to those exposed to them on a regular basis.

9.07.9.5 Soils

Soils can exhibit a complex range of physical, mineralogical, and chemical characteristics that depend on many interrelated factors such as parental rock composition and mineralogy, climate, topography, vegetation amounts and types, water infiltration versus runoff, soil moisture, organic matter, amounts and types of anthropogenic contaminants, and many others. As a result, the bioreactivity, bioaccessibility, and biodurability of bulk soils can vary widely. Potential role of soils in human health has been discussed extensively (e.g., Oliver, 1997; Selinus, in press; see references in Appleton *et al.*, 1996; Ruby *et al.*, 1999). Two examples here illustrate the geochemical interactions between soils and body fluids.

9.07.9.5.1 Soils and neurodegenerative diseases

Although aluminum is typically poorly absorbed via either inhalation or ingestion routes (Goyer and Clarkson, 2001), uptake of bioaccessible aluminum has been speculated to be one of several possible causes for some degenerative neurological diseases such as Alzheimer's disease, Parkinsonism Dementia Complex (PDC), and amyotrophic lateral sclerosis (known as Lou Gehrig's disease, or ALS) (Goyer and Clarkson, 2001).

Epidemiological clusters of PDC–ALS on Guam were first recognized in the early 1940s. Epidemiological studies there have essentially ruled out a genetic cause for the diseases (Perl, 1997), and indicate a link to environmental factors. Incidence of PDC–ALS on Guam has diminished since the 1940s (Garruto *et al.*, 1985; Perl, 1997). The diseases are rare on the northern portions of the island that are underlain by limestones. They are much more prevalent on the southern volcanic portions of the island. A potential link to bedrock, soil, and water geochemistry has been proposed as a result of greater acid weathering on the volcanic-derived soils than on the more alkaline, limestone-derived soils, leading to a decrease in available calcium and magnesium in soils and waters, and an increase in available aluminum via either inhalation or ingestion uptake of soil particles (Garruto *et al.*, 1985, 1989; Crapper MacLachlan *et al.*, 1989).

Miller and Sanzolone (2002) subjected samples of both volcanic- and limestone-derived soils from Guam to detailed bulk chemical analysis and several types of chemical leach tests, including a leach test using SLFs. The leach tests indicated that, contrary to results of earlier studies, little aluminum is readily leached from the soils, but that calcium is readily leached. Based on these results, bioaccessible aluminum from soils does not appear to be a viable etiologic agent for the elevated PDC and ALS occurrences on Guam. However, manganese (a known neurotoxin), silica, barium, cobalt, nickel, uranium, and vanadium can be leached, depending upon the particular soil sample, in substantial quantities; these elements may warrant further investigation for their potential health effects.

9.07.9.5.2 Soil-borne pathogens

As summarized by Bultman *et al.* (in press), a number of soil-borne pathogens have been linked to a variety of diseases, including protozoa, bacteria, fungi, viruses, and prions. Pathogens considered to be soil-borne include those that complete all or some of their life cycles in soils, and those whose life cycle is spent primarily in other organisms but that can survive for some period of time if released into soils from their hosts. Depending upon the particular pathogen, exposure can result from inhalation of dusts

generated from soil, direct or incidental (i.e., on foodstuffs) ingestion of soil, dermal contact with soil, and/or ingestion of water containing pathogens washed from soil. A few examples of soil-borne pathogens and their associated diseases include (Bultman *et al.*, in press; Griffin *et al.*, 2002): *Coccidioides immitis*, a soil fungus that causes Valley Fever, or coccidioidomycosis; *Aspergillus* spp., various species of a fungus found in soils, dusts, and waters that cause aspergillosis and increased asthma; *Bacillus anthracis*, a well known soil bacteria, which causes anthrax; *Hantavirus* spp., various species of viruses that cause Hantavirus pulmonary syndrome

As described by Bultman *et al.* (in press), the viability of soil microbes while in the soil can be significantly affected by a variety of soil characteristics, including: grain size; pH; water content; presence or absence of abundant organic matter, clays, or soluble salts. For example, *C. Immitis*, the etiological agent for valley fever, is endemic in much of the arid US southwest and in parts of South America, in hot, seasonally dry climates with short winters. It seems to be most abundant, and hence best competes against other microbes, in soils that: are alkaline; have abundant pore spaces; have $<10\%$ clay-sized material; have low amounts of organic matter; occur in seasonally wet/dry, hot climates; have elevated salinity, with abundant soluble evaporative salts; and, may have borate salts, which may act as antibiotics for bacteria that compete with the fungus.

It is interesting to speculate whether soil minerals that help enhance the viability of a pathogen in the soil can also help to enhance the pathogen's ability to infect a human. For example, alkaline soluble salts that favor *C. Immitis* in soils might, if inhaled, also be reactive enough to make the lung fluids more alkaline, thereby providing a more hospitable environment in which the spores could take hold to trigger valley fever. In addition, it is possible that elements or metals in the salts, such as boron, might also be toxic to the macrophages, thereby diminishing the body's ability to clear the spores.

9.07.9.6 Dusts Generated by the World Trade Center Collapse

The tragic attacks on and collapse of the World Trade Center (WTC) towers in New York City on September 11, 2001, generated a massive dust cloud that enveloped much of lower Manhattan. The dust cloud left behind deposits of dust, debris, and paper up to many inches thick, both outdoors and indoors in rooms where windows were open at the time of the collapse or (in the case of buildings close to Ground Zero) that were blown open by the force of the collapse.

Concerns immediately developed regarding the potential health risks associated with exposure to the dusts generated by the initial collapse and subsequent months of cleanup, as well as smoke from fires that smoldered within the debris at Ground Zero for some weeks after the attacks. A variety of health problems and toxicological effects have been documented to date (Stephenson, 2002; Gavett *et al.*, 2002; Prezant *et al.*, 2002; Scanlon, 2002; Rom *et al.*, 2002; Landrigan *et al.*, 2002; Landrigan, 2001). These include:

- short-term effects of dust exposure, such as intense burning of the eyes, mouth, and upper respiratory tract, nasal congestion, and gagging reflux of incidentally swallowed dust;
- sinusitis, laryngitis;
- development of the "WTC Cough," a persistent cough developed after prolonged exposure;
- other respiratory effects, such as shortness of breath, chronic chemically induced bronchitis, new-onset asthma, exacerbation of existing asthma;
- chemical pneumonitis (rare, three cases);
- acute eosinophilic pneumonia (rare);
- corrosive damage to and irritation of respiratory tract; and
- gastroesophageal reflux disease, resulting from corrosive damage to the gastrointestinal tract.

A number of excellent studies have been carried out to characterize the materials and chemical composition of settled dust deposits and airborne dust, smoke, and other aerosols generated by the WTC collapse (Lioy *et al.*, 2002; Lioy, 2002; Thurston *et al.*, 2002; Millette *et al.*, 2002; Chatfield and Kominsky, 2001; Clark *et al.*, 2001; USGS, 2002; Plumlee *et al.*, 2002). The following discussion is taken largely from results of USGS studies of settled dust deposits (Clark *et al.*, 2001; USGS, 2002; Plumlee *et al.*, 2002; Plumlee and Ziegler, unpubished data). Results of other studies are also cited where they provide information not obtained in the USGS study.

The settled dusts are quite heterogeneous in materials makeup, particle size, and chemical composition, both from sample to sample across lower Manhattan, and within a given sample down to the micrometer scale. The dusts are composed of particles of a wide variety of materials used in building construction and that are found within office buildings, including: glass fibers (mineral wool or slag wool used in ceiling tiles and insulation), gypsum (from wallboard), concrete, glass shards, paper, rock-forming minerals such as quartz (from aggregate in concrete, dimension stone and other sources), iron-rich particles (from steel beams and other sources), zinc-rich

particles (presumably from metal ductwork), lead-rich particles (solder, lead oxide from paints), and others.

Chrysotile asbestos was found in most settled dust samples at levels generally less than 1%, but in levels as high as 20% by volume in material coating a steel beam in the debris at Ground Zero. Low levels of amphibole asbestos fibers were identified only in one settled dust sample collected north of the WTC complex (Chatfield and Kominsky, 2001).

Lioy *et al.* (2002) and Thurston *et al.* (2002) found that the dominant particle size of the settled dust samples is in the 2.5 μm to tens of μm range. These particles, if inhaled, would tend to be trapped in the uppermost portions of the respiratory tract. They found little asbestos in the <2.5 μm fraction of settled dust samples.

The major-element compositions (silicon, sulfur, magnesium, aluminum, iron, carbon) of the dusts represent the contributions of glass fibers, concrete, gypsum wallboard, metals, paper, and other materials within the office buildings (Clark *et al.*, 2001). Trace-element compositions enriched in a variety of metals (zinc, barium, lead, copper, chromium, molybdenum, antimony, titanium) reflect contributions from paints, lighting, electrical wires, pipes, computer equipment, electronics, and other diverse materials. Many of these metals are substantially enriched in the settled dust samples compared to soils of the eastern United States (USGS, 2002), and some, such as lead, are in some samples in excess of recommended residential soil standards set by some states (Sittig, 1994). Lioy *et al.* (2002) found a wide variety of organic chemicals in bulk settled dust samples (not separated by size), including polycyclic aromatic hydrocarbons, polychlorinated biphenyls, and many others.

Chemical leach tests on the bulk settled dust samples showed that the dusts are quite chemically reactive. Leach solutions have high alkalinities, due to the rapid partial dissolution of calcium hydroxide from concrete particles. Indoor dust samples produced higher pH levels (11.8–12.4) and alkalinities (~600 mg L^{-1} $CaCO_3$) than outdoor dusts (pH 8.2–10.4; alkalinity ~30 mg L^{-1} $CaCO_3$), indicating that outdoor dust samples had reacted with rainfall or other water prior to collection. Thurston *et al.* (2002) found that the leachate pH of the dusts decreased with decreasing particle size. Some metals or metalloids in the dusts (aluminum, chromium, antimony, molybdenum, barium, copper, zinc, cobalt, nickel) are readily leached by deionized water; many of these form oxyanion species or carbonate complexes that are most mobile at the alkaline pH's generated by the leachates.

Our recent chemical leach tests on settled dust samples using deionized water and SLF as the extracting fluids provide further insights into the potential chemical behavior of the dusts *in vivo* (Figures 11 and 12). The SLF produce smaller pH shifts than deionized water due to the buffering capacity of the SLF components (Figure 11). The concentration of phosphate in the SLF drops substantially, probably due to reactions with calcium released from the concrete particles and the resulting precipitation of insoluble calcium phosphate minerals. Metals such as copper and zinc are even more soluble in SLF than in water due to complexing with chloride, citrate, and glycine (Figure 11). The tests do not indicate that lead can be substantially dissolved from the dusts by either water or SLF, possibly because the lead occurs in relatively insoluble phases in the dusts and/or forms insoluble phosphate precipitates. Chemical speciation calculations of the leachate fluids produced by the SLF (Figure 12) indicate that the extraction fluids are highly supersaturated with a wide variety of silicates, including chrysotile and amphiboles.

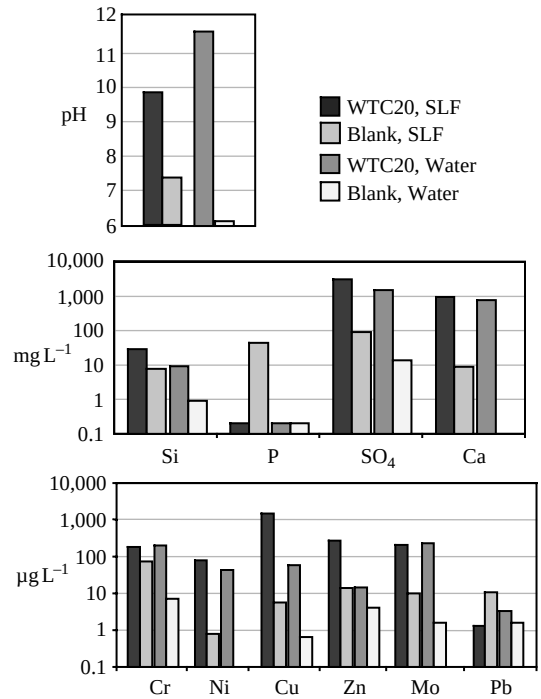

Figure 11 Plots comparing results of water and SLF leach tests performed on settled dusts generated by the WTC collapse. One part dust is added to 20 parts water or SLF at 37 °C and mixed for 24 h, with the leachate filtered (<0.45 μm) and analyzed. The composition of the SLF used in the extraction is a variation on the recipe provided by Bauer *et al.* (1997): pH 7.4; Na—150.7 mM; Ca—0.197 mM; NH_4—10 mM; Cl—126.4 mM; SO_4—0.5 mM; HCO_3—27 mM; HPO_4—1.2 mM; Glycine—5.99 mM; Citrate—0.2 mM. Other metals shown in the SLF blank were contributed as trace constituents of the various chemical reagents used to make up the fluids.

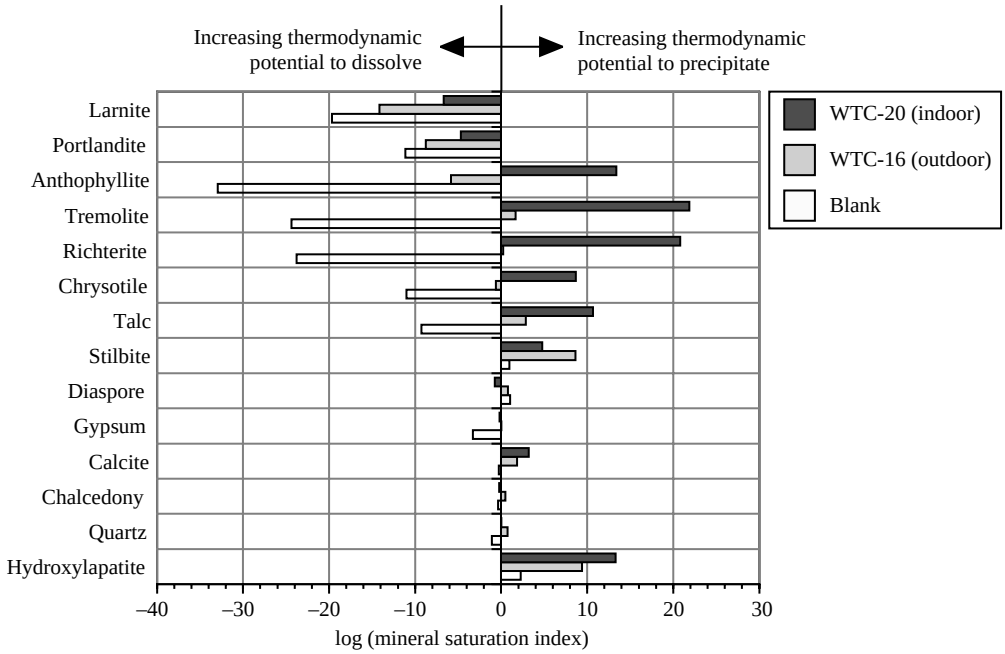

Figure 12 Plot comparing calculated saturation indices of various minerals of interest in SLF blank, and filtered (<0.45 μm) SLF leachates of an indoor WTC dust sample (WTC-20) and outdoor WTC dust sample (WTC-16). The extreme supersaturations in the WTC dust leachate samples may result in part (but not entirely) from inclusion of some colloidal material less than 0.45 μm in size in the analyzed filtrate.

In summary, the settled dusts generated by the WTC collapse are a complex and heterogeneous mixture of bioreactive, bioaccessible, and biodurable particles. Results of chemical leach tests using water and SLF indicate that a variety of chemical reactions may have occurred as inhaled dusts encountered fluids lining the respiratory tract. Although indications are that most particles were too coarse to reach the alveoli, highly alkaline concrete particles likely triggered the generation of caustic alkalinity where they came into contact with body fluids; this alkalinity is thought to have been the major cause of the chemically induced irritation of the eyes, mouth, throat, upper respiratory tract, and gastrointestinal tract (Stephenson, 2002). A variety of metals and metalloids, especially those mobile under relatively alkaline conditions, were probably also released from the dusts; it is unclear what, if any, toxicity such metal releases may have caused. Chemical reactions between the body fluids and the dust constituents may have triggered precipitation of secondary phases in the respiratory tract such as calcium and lead phosphates. Finally, the presence of readily soluble, alkaline material in the dusts may have enhanced the chemical stability of biodurable particles such as asbestos fibers in the respiratory system; however, it is unclear whether this enhanced stability would persist over the long term as the more soluble components of the dusts are removed by interaction with successive aliquots of lung fluids.

Perhaps most importantly, these results show that the potential health effects of complex earth materials cannot be assessed based solely on the toxicity of their together individual components—the integrated effects of the whole material must be considered, along with potentially complex chemical interactions between individual components and the body's fluids.

9.07.10 SUMMARY

In this chapter, we have provided an overview of the myriad potential geochemical and biochemical processes, coupled with their potential links to toxic responses, which can occur when earth materials come into contact with body fluids via inhalation, ingestion, or percutaneous exposure routes.

It is possible to group the health effects resulting from exposures to earth materials according to similarities in how the health effects originate:

- effects that result primarily when bioreactive earth materials substantially modify the chemical composition of body fluids and tissues (such as alkali or acid burns);
- effects that result from the solubilization of bioaccessible toxins from earth materials and the subsequent absorption, metabolism, and effects of the toxins in the body;

- effects that result from the exposure to earth materials that are insoluble (biodurable) in body fluids, and that trigger toxic responses as the body attempts to clear the materials;
- effects that result from pathogens associated with earth materials; and
- effects that result from the body's immune response to the earth materials or toxins contained within the earth materials.

Important unifying threads between most, if not all, of these different these types of health effects are that they:

- can be influenced strongly by the forms in which potentially toxic earth materials occur as they are delivered to the body (mineralogy; particle size and morphology; particle solubility, alkalinity, acidity; oxidation state of contained constituents; etc.) and
- ultimately require some level of chemical interactions between the earth materials and body fluids.

Both of these unifying threads implicitly require important roles for the earth scientist in helping to both characterize earth materials and understand geochemical processes in the context of the human body. In spite of the many *in vitro* and *in vivo* studies that have been carried out to address this complex but fascinating topic, there are many unresolved questions remaining, and therefore abundant opportunities for fruitful future collaborations between geochemists and their colleagues in the toxicology, chemical physiology, epidemiology, and other medical fields.

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