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The Toxicological Geochemistry of Earth Materials: An Overview of Processes and the Interdisciplinary Methods Used to Understand Them

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INTRODUCTION

A broad spectrum of earth materials have been linked to, blamed for, and/or debated as sources for disease. In some cases, the links are clear. For example, excessive exposures to mineral dusts have long been recognized for their role in diseases such as: asbestosis, mesothelioma, and lung cancers (asbestos); silicosis and lung cancer (silica dusts); and coal-workers pneumoconiosis (coal dust). Lead poisoning, particularly in toddlers and young children, has been conclusively linked to involuntary ingestion of soils or other materials contaminated with lead-rich paint particles, leaded gasoline combustion byproducts, and some types of lead-rich mine wastes or smelter particulates. Waters with naturally elevated arsenic contents are common in many regions of the globe, and consumption of these waters has been documented as the source of arsenic-related diseases affecting thousands of people in south Asia and other regions. Exposure to dusts or soils containing pathogens has been documented as the cause of regionally common diseases such as valley fever (coccidioidomycosis) and much rarer diseases such as anthrax. Links between many other earth materials and specific diseases, although suspected, are less clear or are debated. For example, it has been suggested that geographic clusters of diseases such as leukemia are related to exposures to waters or atmospheric particulates containing organic or metal contaminants; however, for many clusters the exact causal relationships between disease and environmental exposure are difficult to prove conclusively. Even for many diseases in which the causal relationship is clear, such as in asbestosis and mesothelioma triggered by asbestos exposure, the minimum exposures needed to trigger disease, the influence of genetic factors, and the exact mechanisms of toxicity are still incompletely understood and are the focus of considerable debate within the public health community. Hence, understanding the health effects resulting from occupational and environmental exposures to a wide variety of earth materials remains a very active and fruitful area of research.

As noted in previous papers (Fubini and Areán 1999; Plumlee and Ziegler 2003, 2006), the body interacts both physically and chemically with earth materials to which it is exposed

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(and which it may take up) via inhalation, ingestion, and dermal absorption. Although these interactions are ultimately physiological, they are also strongly influenced by the physical and chemical properties of the earth materials, coupled with their geochemical reactivities in the variety of water-based, chemically diverse body fluids (respiratory, gastrointestinal, perspiration, blood serum, interstitial, and intracellular fluids) encountered along the different exposure and uptake pathways. As a result, there are significant opportunities for earth scientists working in collaboration with health scientists to contribute expertise in mineralogy, materials characterization, fluid-mineral reactions, and other areas in the quest for a better understanding of the specific links between earth materials and human health. In order to emphasize the importance of such interdisciplinary approaches, Plumlee and Ziegler (2006) defined toxicological geochemistry (TG) as the study of the geochemical interactions between body fluids and earth materials, and how these interactions may influence toxicity.

This chapter first provides an overview of the processes by which earth materials interact with the body. We then describe how earth science expertise and methods can be applied collaboratively throughout the range of heath science characterization and assessment methods commonly used to understand health issues associated with exposure to and uptake of earth materials. This paper is intended to complement and update the discussions presented in Plumlee and Ziegler (2003, 2006). As with these two earlier papers, we hope that readers from both the earth science and health science communities will find this chapter useful in understanding how geochemical processes and principles can be applied to help understand links between human health and exposures to certain earth materials. Our intent is to not imply that all earth materials are hazardous to health, as this is clearly not the case. Rather, we instead hope to show how a healthy dose of earth science expertise can be used to help understand where potential problems exist and help define the nature of the problems. We also hope that this paper and the many excellent other papers presented in this interdisciplinary volume will help identify and inspire future opportunities for fruitful research collaborations between geochemists, other earth scientists, and their counterparts in the health science community.

EARTH MATERIALS LINKED OR POTENTIALLY LINKED TO HUMAN HEALTH

Earth materials can include a broad range of solid, gaseous, or liquid substances that are produced and released by natural earth processes, that are contaminated by and/or released from the earth as a result of human activities, or that are produced from the earth by humans and transformed for use in society (Fig. 1). Examples of earth materials with known or postulated health concerns are listed in Table 1. The health concerns have a variety of origins, and can result from the earth materials themselves (such as mineral dusts), from contaminants or pathogens contained within or carried by the earth materials, and from consumption of waters, plants, or organisms that have picked up contaminants by interacting with earth materials. The potential health concerns are quite diverse, and can include cancers, respiratory diseases, neurological diseases, diseases of the excretory system, secondary diseases such as congestive heart failure, increased susceptibility to pathogen infections, and many others.

Historically, studies examining the toxicity and health effects of earth materials primarily focused on materials to which humans were exposed in workplace settings (such as asbestos or crystalline silica), or on soils or other earth materials containing toxicants of known health concern (such as lead, mercury, arsenic, or hexavalent chromium). Toxicological studies focused, for example, on commercially-produced asbestos or silica, or on the processes controlling toxicity of soluble metal salts or other materials common in workplace exposures. In the last several decades, there have been increasing concerns regarding environmental exposures to earth materials that a) are released into the environment by natural or anthropogenic processes, b) contain potential toxicants in more complex mineralogical forms than simple salts, or c)

Figure 1. There is a continuum of interactions between the earth's geosphere, hydrosphere, biosphere, atmosphere, and anthropogenic activities that all can produce earth materials or environmental materials to which humans can be exposed and that may be of potential health concern.

contain other elements such as antimony, tungsten, selenium, vanadium, or others whose toxicity effects are less well-known.

FACTORS INFLUENCING THE HEALTH EFFECTS OF EARTH MATERIALS

For detailed discussions on the toxicity effects of a wide variety of potential toxicants, the interested reader is referred to several excellent toxicology textbooks (such as Klassen 2001; Sullivan and Krieger 2001). Discussions focused on earth materials are presented by Plumlee and Ziegler (2003, 2006).

There are many different factors that can influence the health effects of earth materials, including:

- Intensity and duration of the exposure (the dose).
- Exposure route.
- Chemical conditions encountered along the exposure route.
- Physical and chemical characteristics of the material.
- The potential microbial or other pathogens present in the material.

Table 1. Examples of earth materials and their sources with known or postulated health effects, modified from Plumlee and Ziegler (2003, 2006).

Material	Examples of potential exposure sources	Primary exposure routes Health effects	References
Asbestos	Dusts from industrial, commercial asbestos products (insulation, brake linings, building products, others) and industrial activities. Dusts from asbestos accessory minerals in other industrial/commercial products (some, but not all, vermiculite, talc, and other products). Dusts from natural asbestos-bearing rocks and soils (via natural weathering and erosion or human disturbance) may provide low-level exposures that may be of concern to chronically exposed populations.	*Inhalation.* Asbestosis; lung cancer; pleural effusion, thickening, plaques; mesothelioma cancer. Associated secondary illnesses include heart failure, other cardiovascular problems, lung infection, possible autoimmune responses. *Ingestion.* Has been proposed as a trigger of GI cancers, other health effects; however, links have not been demonstrated with certainty.	Skinner et al. (1988); Holland and Smith (2001); Pfau et al. (2005); Pan et al. (2005); Dodson and Hammar (2006); Roggli et al. (2006).
Crystalline silica	Dusts generated by mining, sandblasting, and other industrial or workplace activities. Dusts produced by erosion of friable, silica-rich rocks (i.e., some ash flow tuffs, diatomaceous earth deposits) may also play a role in disease.	*Inhalation.* Silicosis, industrial bronchitis with airflow limitation, progressive massive fibrosis. Associated illnesses include opportunistic infections, silica nethropathy, lung cancer.	SSDC (1988); Castranova and Vallyathan (2000); Castranova (2000); Daroowalla (2001)
Coal dust, coal fly ash, coal combustion gases	Dusts, other aerosols, and gases generated by coal mining, processing, and combustion activities.	*Inhalation.* "Black lung disease" includes Coal Worker's Pneumoconiosis (CWP), progressive massive fibrosis, chronic airway obstruction or bronchitis, emphysema; possible silicosis due to intermixed crystalline silica. Sulfur dioxide and volatilized arsenic released as a result of coal combustion have also been linked to health effects.	Castranova and Vallyathan (2000); Castranova (2000); Daroowalla (2001);
Other commercial and industrial mineral dusts	These include talc, kaolinite, other clays, micas, and aluminosilicates. Sources include dusts generated from industrial and commercial activities and products	*Inhalation.* Mineral-specific fibrosis, such as talcosis; also silicosis and asbestosis due to intermixed crystalline silica and asbestos.	Daroowalla (2001)

(table continued on next page)

Table 1. *(continued)*

Material	Examples of potential exposure sources	Primary exposure routes Health effects	References
Natural mineral dusts	Dusts generated from desert areas, dry lake beds, agricultural areas during dry periods.	*Inhalation.* Possible silicosis, asbestosis. Possible uptake of metals or metalloids such as arsenic. Possible exposure to organic contaminants or pathogens in the dusts	Derbyshire (2005)
Urban particulates	Atmospheric particulates generated by petroleum or coal combustion, construction/demolition, industrial emissions, disturbance of urban soils, many others.	*Inhalation.* Possible uptake of heavy-metal and organic toxicants. Inhalation of acid aerosols of sulfur dioxide. Inhalation of irritant and/or oxidant gases such as nitric oxides and ozone. Increased asthma and cardiac stress, decreased lung function.	Costa (2001)
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.	Hesterberg et al. (2001)
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, although some heavy metals such as thallium or hexavalent chromium may be present. Silicosis maybe a concern with long-term exposure to concrete dust.	Sahai (2001)
Edible soils	Soils purposefully consumed by humans as a result of cultural practices or perceived nutritional needs.	*Ingestion.* Potential uptake of heavy metals or other toxicants. Secondary physiological problems associated with consumption of non-digestible mineral material.	Abrahams et al. (2005)

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Table 1. *(continued)*

Material	Examples of potential exposure sources	Primary exposure routes Health effects	References
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 within ash.	Weinstein and Cook (2005), and their references.
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.	Weinstein and Cook (2005), and their references.
Wildfire smoke, and ash	Particulate matter (including smoke, ash, and fine soil particulates) and gases generated by forest fires.	*Inhalation.* Asthma, irritation of respiratory tract; possible increased susceptibility to infection of respiratory system; possible long term increased cancer risk. Most studies have focused on organic constituents of smoke; less work has been done on mineral particles and heavy metals in smoke.	Reinhardt and Otmar (2000); Reinhardt et al. (2000); Ward (1999); Wolfe et al. (2004)
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.	Bultman et al. (2005)

- Biosolubility, biodurability, bioaccessibility, and bioreactivity of the material in the body fluids encountered along the various exposure routes.
- The body's immune response.
- The body's physiological processes that control absorption, distribution, metabolism, and excretion of toxicants.
- Other confounding factors, such as age, gender, genetics, personal habits (i.e., smoking), and personal socioeconomic, health, nutritional status, and dietary cofactors that may promote or counteract the toxic effects of the exposure.

Intensity and duration of exposure (the dose)

To paraphrase an observation first made by Paracelsus in the 1500's, "*everything is a poison, nothing is a poison, it is the dose that makes the poison*." In its simplest definition, the dose is the amount of a potential toxicant that is taken up by an organism over a given period of time, with dose-response indicating that the greater the amount of a toxicant taken up by an organism, the greater the toxicological effect (Rozman and Klaasen 2001). However, toxicity is ultimately more complicated in that it is a function of the amounts of a potential toxicant that are taken up by the body, that survive the body's many clearance and mitigation mechanisms, and that reach the particular site(s) of toxic action within the body. Each substance will have a threshold level above which it will become toxic that depends on the substance, the exposure route, and the individual (Sullivan et al. 2001). Substances can be acutely toxic, if the dose is sufficiently high over a short period of time, and/or chronically toxic, where the dose is lower but over a longer period of time. A wide variety of chemical elements, including major chemical species (sodium, calcium, potassium, etc.), and trace elements (zinc, copper, selenium, chromium, etc.) are essential to the effective functioning of the body, and so disease can result if these elements are deficient in the body; however, they can also become toxic if present in excess in the body (Lindh 2005a,b).

Exposure route

There are several major exposure routes via which individuals can come into contact with potential toxicants or pathogens. These include inhalation, ingestion, and direct contact through unbroken skin (percutaneous), eyes (ocular), or wounds. A given toxicant or pathogen can have very different effects depending upon the exposure route due to the differences in physical processes, physiological processes, and chemical conditions to which it is subjected along each of the pathways (Fig. 2).

Inhalation. A variety of physical, chemical, and physiological processes within the respiratory tract affect the ultimate disposition and health effects of inhaled earth materials (see overviews by Schlesinger 1988, 1995; McClellan and Henderson 1995; Fubini and Areán 1999; Gehr and Heyder 2000). Important disposition mechanisms include deposition, clearance, retention, and, for gases or soluble materials, absorption. The characteristics of an inhaled earth material play a complex but important role in its disposition, including: the type of material inhaled (solid, liquid, gas, or pathogen); the concentrations of the material in the inhaled air; the chemical composition of the material; the solubility and reactivity of the material in the fluids lining the respiratory tract; and, for solids, their shape, size distribution, density, and surface charge.

Solid particles that deposit in approximately the first twelve generations of airways (which are lined by ciliated epithelium) are cleared by mucocilary clearance. Rhythmically-beating cilia waft the particle on a mucociliary escalator to the pharynx, where it is then swallowed. Particles depositing in more distal generations are subject to alveolar clearance, which is believed to occur primarily through phagocytosis by alveolar macrophages.

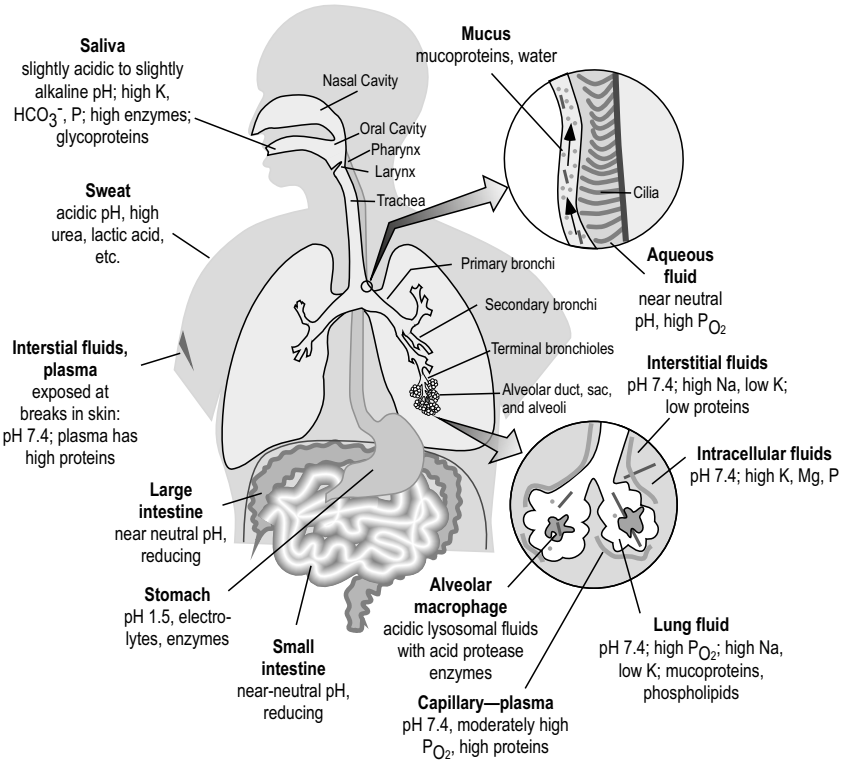

Figure 2. This schematic diagram, modified from Plumlee and Ziegler (2006), illustrates the various exposure routes and the substantial variability in body fluid types and compositions that can be encountered by earth materials during exposure.

The respiratory tract airways are lined with two liquid phases that facilitate deposition and clearance of solid particles: these include a mucous phase containing glycoproteins and phospholipid surfactants, and an underlying aqueous electrolyte phase. Mechanisms of particle deposition include (Fig. 3; Schlesinger 1988, 1995):

- impaction on the airway walls at places where there are rapid changes in airflow direction (such as at branches or constrictions in the airway);
- sedimentation onto the airway walls due to gravity settling;
- electrostatic deposition of freshly generated particles with high surface charges;
- interception of elongated particles by the airway walls;
- deposition of fine particles (<0.2 μm) as a result of brownian diffusion–impaction of air molecules on the particles enhances random motion that increases the likelihood of deposition on airway walls.

Figure 4 illustrates the influence of size in determining particle deposition efficiency in the various levels of the respiratory tract; other factors include, for example individual particle density and breathing patterns in the exposed individual. During normal nasal breathing, the largest inhaled particles (from ~5 to greater than several tens of microns large) are deposited in the nasopharyngeal airways (Fig. 4; ICRP 1995). Progressively smaller particle sizes are more

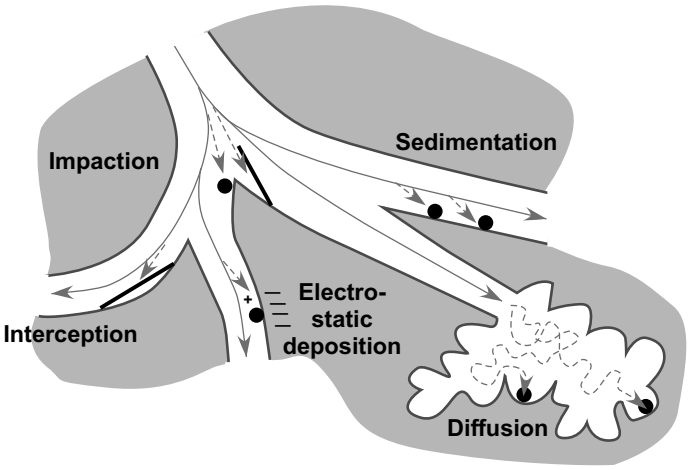

Figure 3. This schematic diagram illustrates various mechanisms by which particles (black) are deposited onto the linings of the respiratory tract. Airflow trajectories are depicted by the solid arrows, and the trajectories followed by deposited particles are shown by dashed arrows. Modified from McClellan (2000).

efficiently deposited in successively deeper portions of the respiratory tract. Particles less than approximately 2 μm (aerodynamic equivalent diameter) in diameter 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.

The airways are close to or at saturation with water (Fubini and Areán 1999). Inhaled particles are therefore fully exposed to water vapor. One effect of the water vapor is to enhance particle clumping, which can enhance deposition higher in the respiratory tract (Schlesinger 1988).

During exercise or conditions where the nasal passages are clogged, or in certain individuals, increased oral breathing can shift the deposition of coarser particles to the upper portions of the trachea, and also can result in increased deposition efficiency of substantially larger particles in the tracheobronchial area (10's of μm) and in the alveoli (3-5 μm) than during normal nasal breathing (Schlesinger 1988). Airway irritation and obstructive airway diseases tend to constrict airways and lead to greater deposition higher in the respiratory tract and reduced deposition in the alveoli (Schlesinger 1988; Schulz et al. 2000). Fibers can behave somewhat differently during inhalation than more equant particles in that, although they tend to flow aerodynamically, wobble along their long axis gives them a larger effective diameter. As a result, only fibers less than approximately 0.5-1.5 μm wide can penetrate into the deepest portions of the alveoli. Also, straighter and shorter fibers tend to escape deposition by interception more readily and so are able to penetrate more deeply into the respiratory tract than curly or long fibers.

Clearance of deposited particles and pathogens from the respiratory tract is accomplished by a variety of mechanisms that are an integral part of the body's immune system, and that can vary as a function of location within the respiratory tract and the physical and chemical nature of the particle (Fig. 3):

- *Increased mucus production:* As hay fever suffers well know, one of the body's immune response mechanisms to inhaled particle overload is to increase production of mucus and fluids in the nasal passageways and upper respiratory tract. This helps

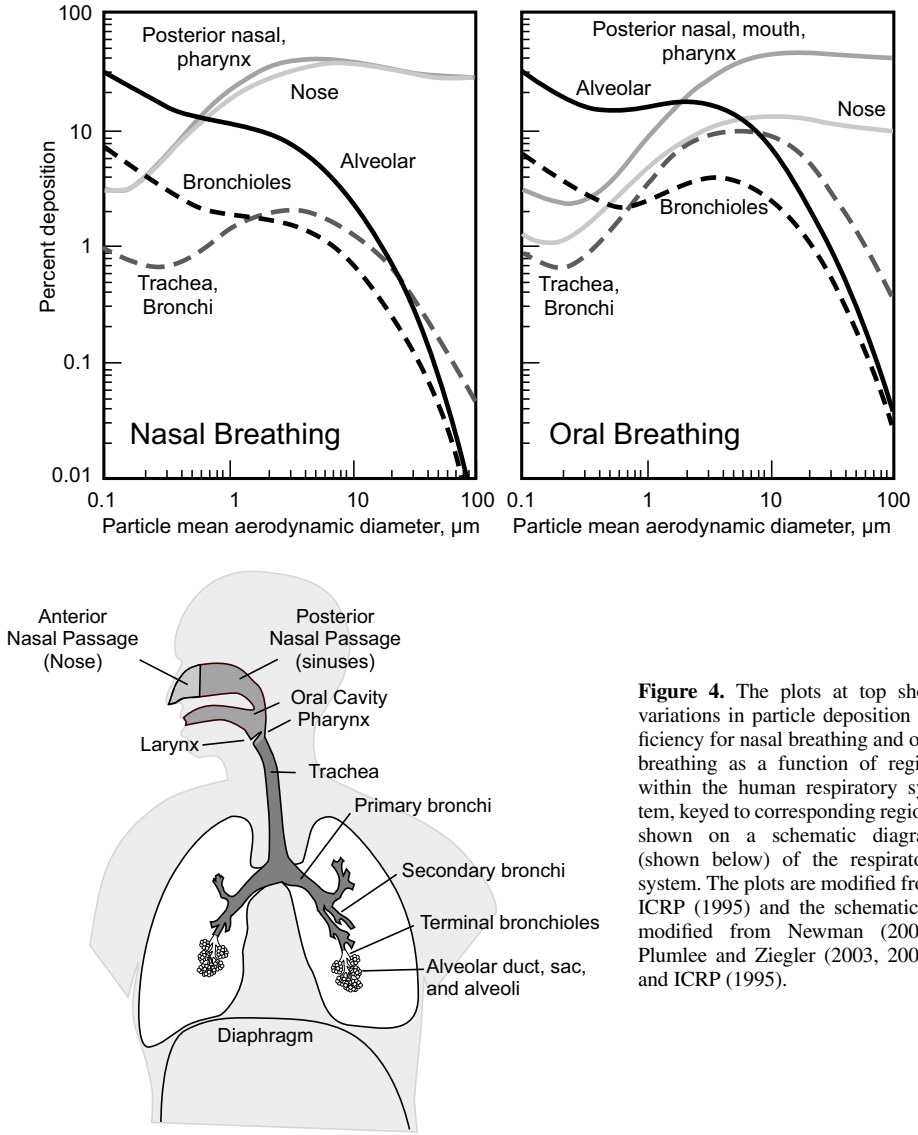

Figure 4. The plots at top show variations in particle deposition efficiency for nasal breathing and oral breathing as a function of region within the human respiratory system, keyed to corresponding regions shown on a schematic diagram (shown below) of the respiratory system. The plots are modified from ICRP (1995) and the schematic is modified from Newman (2001), Plumlee and Ziegler (2003, 2006), and ICRP (1995).

trap particles in the upper parts of the respiratory system and also helps to dilute chemical effects of inhaled particles on adjacent tissues.

- *Coughing:* Particle-laden mucus is cleared from the trachea and bronchi in part by coughing, especially in individuals with respiratory disease or irritation.
- *Mucociliary transport:* The cells lining the trachea, bronchi, and bronchioles are ciliated. Movement of the cilia helps transport the particle-laden mucus up and out of the respiratory tract along the mucociliary escalator, and the cleared mucus is then either expectorated or swallowed.
- *Dissolution in the fluid lining the respiratory tract:* Soluble particles or gases are

cleared primarily by dissolution in the near-neutral pH fluid lining the airways at all levels of the respiratory tract. The dissolved materials are relatively efficiently absorbed into the bloodstream.

- *Phagocytosis by airway and alveolar macrophages:* Macrophage cells roam the fluids lining the respiratory tract and engulf (phagocytize) foreign particles (Kreyling and Scheuch 2000). Airway macrophages in the tracheal and bronchial airways play a subsidiary role in particle clearance compared to the mechanisms listed previously, whereas alveolar macrophages play a primary role in particle clearance from the alveoli. The macrophages contain lysosomes with acidic pH and digestive enzymes such as acid hydrolases (Brain 1992; Newman 2001), and so can help dissolve less soluble particles that had not previously dissolved in the fluids lining the respiratory tract. The dissolved material can either be transported out of the macrophage, or may react with cellular components and remain in the macrophage. The macrophages can also transport engulfed particles to the mucociliary elevator, to distal alveolar spaces (sequestration), or through the lung epithelium to the lymph system or the pleural spaces. Once the macrophages phagocytize particles, they also release chemical messengers called cytokines into the surrounding epithelium that recruit other macrophages to the site to aid in the clearance of additional foreign particles (Lehnert 1992). The macrophages, which are 5-10 μm in diameter, can only engulf particles smaller than 2-5 μm (Fubini and Areán 1999). Therefore, long fibers that reach the alveoli are less readily cleared than more equant particles of the same aerodynamic diameter, because they cannot be easily engulfed by the alveolar macrophages. A process called frustrated phagocytosis results when the macrophages that fail to engulf a fiber die and release their cytotoxic chemicals into the surrounding cellular environment, potentially leading to injury to adjacent cells. Fibers or particles with sharp points can also penetrate the macrophages' cell membranes, which also can cause leakage of cytotoxic chemicals into the surrounding alveolar spaces (Fubini and Areán 1999).
- *Particle uptake by airway and alveolar epithelial cells:* Phagocytic uptake of free particles by cells lining the airways and alveoli is typically small compared to other clearance mechanisms, but is enhanced if free particles persist, such as during lung overload conditions where the other mechanisms are overwhelmed (Churg 2000).
- *Particle penetration into the interstitial spaces of the lungs:* Particles can penetrate through the epithelial surface lining the alveoli into the pulmonary interstitial spaces, where they can persist, react with the lung interstital fluids, or be engulfed by interstitial macrophages or interstitial cells.

In spite of these many clearance mechanisms, relatively insoluble particles can be retained in the lungs for extended periods of time following a brief acute exposure. However, there are significant differences in the rates which equivalent particles can be cleared by different species. For example, McClellan (2000) indicates that rats have substantially greater particle clearance rates for respired insoluble particles than do humans; such differences are an important consideration in the extrapolation of inhalation toxicology studies based on rats to make inferences about toxicity of the same particles to humans.

The disposition of inhaled gases in the respiratory tract depends upon the gas species present, their concentrations in the inhaled air, and their solubilities in the water-based fluids lining the respiratory tract. Water-soluble gases (i.e., sulfur dioxide) can be absorbed more readily in the upper portions of the respiratory tract, whereas less soluble gases (i.e., nitrogen oxides) are more likely to persist into the alveolar spaces where gas exchange with blood is most effective (Newman 2001). However, even soluble gases may penetrate into the alveolar spaces if the gases are present in sufficiently high concentrations in inhaled air. Gas absorption in the alveoli occurs primarily by diffusion through the epithelial lining and then dissolution

in the blood. Carbon monoxide, hydrogen cyanide, and some other toxic gases preferentially bind with hemoglobin in the blood, thereby precluding uptake of oxygen.

Ingestion. In general, most earth materials are ingested involuntarily, such as through hand-to-mouth contact in toddlers and young children, ingestion of soil particles transported on poorly cleaned foodstuffs, or swallowing of dust particles cleared from the respiratory tract by the mucociliary escalator. In some societies, however, geophagia, the voluntary ingestion of soil, is practiced for nutritional or detoxification purposes (Abrahams 2005).

The gastrointestinal (GI) system includes several major regions that are sequentially traversed by ingested earth materials, each with its own characteristic function, physical processes, and chemical environment. These regions include the mouth, pharynx, esophagus, stomach, small intestine, and large intestine. In addition to its primary function (to intake and digest food, extract energy and nutrients, and expel the remaining waste), the GI tract also is a key component of the body's immune system: for example enzymes and antibodies in the saliva, acid in the stomach, and bacteria in the intestines all help to neutralize ingested pathogens (Coico et al. 2003).

The disposition of ingested earth materials depends upon their particle makeup (the phases present), size distribution, chemical solubility in the fluids encountered along the GI tract, the presence of other material (such as food), and biologically mediated reactions (some of which occur with the participation of resident microbes) that may transform the earth materials and their degradation products (Plumlee and Ziegler 2003, 2006).

Due to physical breakdown during chewing, ingested particles are generally less than 500 μm to 1 mm in size. Chewing helps reduce particle size, and can therefore increase the surface area and reaction rates of the particle in the GI system. Studies of hand-mouth transmission indicate that the largest particles that adhere to hands of toddlers or young children are in the 250-μm size range (EPQ TRW 2000).

Ingested earth materials are progressively subjected to a variety of fluid compositions and chemical conditions along the GI system, starting with near-neutral, enzyme-rich saliva in the mouth, then acidic gastric fluids in the stomach, then near-neutral fluids with pancreatic and bile juices in the small and large intestines (see Table 2, this chapter; also see Plumlee and Ziegler 2003, 2006). The digestive process is initiated by the saliva, which contains enzymes to initiate food breakdown (Table 2). Substantial breakdown and dissolution of ingested substances occurs in the acidic and enzyme-rich fluids of the stomach, whereas most absorption occurs in the intestinal tract (Sipes and Badger 2001). It is important to note that materials that are dissolved in the stomach may not all be absorbed across the intestinal tract lining. For example, those substances that are most readily absorbed by diffusion across the intestinal wall into the bloodstream are in non-ionized, lipid-soluble forms. Further, materials dissolved in the acidic conditions of the stomach may subsequently re-precipitate or adsorb onto solids in the more alkaline environment of the intestines, and then be eliminated as waste. Gastrointestinal absorption of essential trace elements such as zinc, copper, and selenium, as well as toxicants such as lead, can also be enhanced or diminished by the presence or absence of other trace elements and chemicals in the diet (WHO 1996). The venous blood supply of the upper portion of the small intestines (which is responsible for the absorption of nutrients as well ingested toxicants and medications) drains into the portal vein of the liver. The liver can metabolize many of these ingested foreign substances, thereby protecting the rest of the body from exposure, but sometimes at the expense of injury to liver cells (acetaminophen ingestion being the most notorious example).

Exposure via the skin or wounds in the skin. Although the skin is the first line of defense for the immune system against external toxicant insults, percutaneous exposures can be a source of adverse health effects for some earth materials. Some gaseous and liquid chemicals

Table 2. Summary of fluid compositions encountered by earth material particles along the various exposure routes. Most of the fluid compositions are summarized in greater detail by Plumlee and Ziegler (2003, 2006) and references therein. Other citations are listed in the table.

Exposure Route **Region**	**Fluid type(s) composition(s) encountered**
Inhalation	
Head airways	**Nasal fluid:** Contains both mucus with glycomucoproteins and phospholipid surfactant, and an electrolyte phase similar to interstitial fluids with pH near 7.4. The fluids are highly oxygenated (P_{O2} as high as 0.2 atm), but contain various reducing organic couples that are out of equilibrium with dissolved O_2.
Trachea, primary bronchi	**Pulmonary fluid:** Contains both mucus with glycomucoproteins and phospholipid surfactant, and an electrolyte phase similar to interstitial fluids with pH near 7.4. The fluids are relatively oxygenated (P_{O2} decreases from 0.2 atm), but contain various reducing organic couples that are out of equilibrium with dissolved O_2.
Bronchioles	**Pulmonary fluid:** Contains both mucus with glycomucoproteins and phospholipid surfactant, and an electrolyte phase similar to interstitial fluids with pH near 7.4. The fluids are relatively oxygenated (P_{O2} decreases to 0.132 atm), but various reducing organic couples are also present that are out of equilibrium with dissolved O_2.
Alveoli	**Pulmonary fluid:** Contains both mucus with glycomucoproteins and phospholipid surfactant, and an electrolyte phase similar to interstitial fluids. The fluids are relatively oxygenated (P_{O2} around 0.132 atm), but contain various reducing organic couples that are out of equilibrium with dissolved O_2.
Macrophages and epithelial cells	**Intracellular fluid:** A pH 7.1, potassium-phosphate-bicarbonate-magnesium-sulfate electrolyte fluid with lesser chloride, calcium, and sodium. Contains a wide variety of organic acids, proteins, and other organic components. Intracellular fluid is more reduced than interstitial fluid, with redox conditions strongly influenced by reduced/oxidized glutathione.
Macrophage lysosomes (phagocytized particles)	**Lysosomal fluid:** Maintains an acid pH around 4.5, and contains acid proteases, acid phosphatases, and other enzymes. We are not aware of literature sources that report the electrolyte composition.
Interstitial tissues adjacent to airways (penetrated by particles from the alveoli and other airways)	**Interstitial fluid:** A pH 7.4, sodium-chloride-bicarbonate electrolyte fluid with: lesser potassium, magnesium, calcium, and sulfate; relatively oxygenated (P_{O2} 0.02 to 0.13 atm); abundant organic acids amino acids, and other organic ligands; substantially lower concentrations of proteins than the plasma.
Blood (particles can penetrate the lung epithelium and capillary walls).	**Plasma:** A pH 7.4, sodium-chloride-bicarbonate electrolyte fluid with lesser potassium, magnesium, calcium, and sulfate; relatively oxygenated (venous P_{O2} around 0.02 atm; arterial P_{O2} around 0.13 atm); abundant organic acids amino acids, and other organic ligands; high concentrations of proteins.

(table continued on next page)

Table 2. *(continued)*

Exposure Route **Region**	**Fluid type(s) composition(s) encountered**
Ingestion	
Mouth	**Saliva:** Dilute electrolyte fluid (Ritschel and Thompson 1983) whose composition depends upon secretion rate. Saliva produced at low secretion rates is slightly acidic (pH 6.6) with higher potassium and high phosphate; saliva produced at higher secretion rates is slightly alkaline (pH 8) with high sodium, bicarbonate, chloride, and phosphate (Thaysen et al. 1954). Saliva contains mucin and a variety of enzymes such as alpha-amylase, lysozyme, and lingual lipase. It also contains antibacterial compounds such as hydrogen peroxide, thiocyanate, and secretory immunoglobulin A.
Stomach	**Gastric fluid:** Sodium-hydronium-chloride electrolyte fluid, with lesser potassium, calcium, and magnesium. The pH is generally maintained near 1.5, but pH values rise due to neutralization by food. Contains pepsin, lipase, lysozyme, and other enzymes, as well as: largely protonated forms of various amino acids and carboxylic acids; mucoproteins; other proteins; and carbohydrates. Although swallowed air may provide some available oxygen, several references suggest gastric juice is rather reducing, perhaps dominated by abundant ascorbic acid - dehydroascorbic acid redox couple (Sobala et al. 1991); several references indicate H_2S is also common (i.e., Keith et al. 2006), but disagree as to the presence or absence of low-molecular-weight sulfur-bearing organics such as cysteine and glutathione.
Intestinal tract	**Intestinal fluid:** Alkaline secretions are added in upper (duodenal) portions of intestines that help raise pH of food-gastric juice mixture (chyme); the pH ranges from around 6 to greater than 7. Bile salts (to aid in digestion and absorption of lipids) and pancreatic juices (which contain enzymes and other organics to help break down proteins and carbohydrates) are also added in the duodenum. Redox conditions are quite reduced, with H_2S stable.
Percutaneous	
Unbroken skin	**Perspiration:** A relatively dilute sodium-chloride electrolyte fluid with lesser potassium and bicarbonate see references in Plumlee and Ziegler (2003). Na and Cl concentrations increase and Na/K ratio decreases with increasing sweat production rate (Freudenrich 1998). Sweat from apocrine glands in armpits and groin contains proteins and fatty acids (which are decomposed by bacteria to produce body odor), whereas sweat from eccrine glands over the rest of the body does not. Sweat also contains metabolic wastes such as urea, uric acid, ammonia, lactic acid, and ascorbic acid.
Wounds in skin	**Plasma:** See description above. **Interstitial fluid:** See description above.

can be readily absorbed directly through the skin, particularly those that are non-ionic or lipophilic, such as methyl mercury. There has recently been increasing discussion in the biomedical literature regarding the potential for solid metallic or metal-bearing nanoparticles (particularly those used in personal care products) to be absorbed directly through the skin and to therefore present a potential source of toxicity (Tinkle et al. 2003; Gulson and Wong 2006). Some gaseous, aqueous, or solid earth materials can react with the skin or with perspiration on the skin, resulting in allergic reactions, skin irritation, or chemical burns. Examples include allergic reactions (contact dermatitis) triggered by jewelry containing nickel, and caustic burns caused by wet alkaline solids such as cement.

Breaks or wounds in the skin can provide direct access for toxicants and pathogens contained in earth materials to tissues and the bloodstream. For example, it has been postulated that Kaposi's sarcoma endemic in parts of Africa results from dermal exposure to iron-rich soils developed on mafic volcanic rocks; farmers that till the soil barefoot take up micron-sized clay- and iron-rich particles through pores or abrasions in the skin of their feet, leading to dermal damage and impaired immunity to pathogens (Ziegler 1993). Further details of these and other health issues linked to dermal exposures to earth materials are provided in Plumlee and Ziegler (2003, 2006).

Physical and chemical characteristics of the earth material

The previous discussions of exposure route illustrated that the physical and chemical characteristics of an earth material can strongly influence how it is taken up by the body, its disposition within the body, and its health effects.

Physical characteristics. The physical characteristics of an earth material primarily include its form—whether it is solid, aqueous, gaseous, or non-aqueous liquid. For solid materials important physical characteristics also include whether the solid is a glass or crystalline, and its mineralogy, density, size, shape (morphology), and surface charge. These physical characteristics ultimately influence how the materials interact both physically and chemically with the body, and how readily the material can be taken up by the body. For example, a variety of solid-based toxicants can have substantial health impacts if they are inhaled or ingested, but a smaller number of solid toxicants have impacts through dermal contact or through breaks in the skin. In contrast, fluids can trigger effects through dermal contact, inhalation of fine droplets, or ingestion. As discussed in the previous sections, size and density influence the depth to which an inhaled particle can penetrate the respiratory tract. Particle shape can influence the aerodynamic properties of a particle as it is being inhaled, and can influence its clearance from the respiratory tract.

Chemical characteristics. Important chemical characteristics include the types (organic, inorganic), amounts, and speciation of potential toxicants in the earth material as it is delivered to the body. The speciation can include how the toxicant occurs within the material (i.e., tied up within the crystal structure or sorbed onto the surface of a solid), and the oxidation state or chemical speciation of potentially toxic elements within the material (for example ferrous and/or ferric iron; arsenate, arsenite, and/or organo-arsenic; mercurous, elemental, mercuric, and/or methylmercury; hexavalent and/or trivalent chromium). Many elements such as mercury or arsenic have substantially different behavior in the body and, as a result, different toxicity effects, depending upon their oxidation state and chemical speciation. Examples will be presented in a later section; see also the discussion in Reeder et al. (2006, this volume).

Potential microbial, parasitic pathogens present in the earth material

It is well-known that water can be the host to a wide variety of bacterial, viral, protozoan, and multicellular pathogens that are the source of illness in humans, and that these pathogens in water can be present both naturally and incidentally as a result of inputs from humans

or other organisms. Soils, dusts, and some other solid earth materials are also a substantial reservoir for a variety of microbes, microscopic multicellular organisms, and prions (agents of transmissible spongiform encephalopathies, or TSEs); see the review by Bultman et al. (2005). A small percentage of these are pathogenic, including soil bacteria such as *Bacillus anthracis* (which causes anthrax), soil fungi such as *Coccidioidies immitis* (*C. Immitis*, the etiological agent of valley fever), viruses, protozoa such as *Cryptosporidium parvum*, and parasitic helminthes (microscopic worms, such as hookworms and round worms). These pathogens can be permanent (complete their entire life cycle in the soil), periodic, transient, or incidental (resulting from human or animal activities) inhabitants of the soil. Depending upon the particular pathogen, exposure can result from inhalation of dusts generated from soil (Griffin et al. 2002), direct or incidental (i.e., on foodstuffs) ingestion of soil, dermal contact with soil, and/or ingestion of water containing pathogens washed from soil. Many pathogens (such as soil fungus spores, viruses, bacteria, and bacterial spores) are in the appropriate size range to be inhaled and to penetrate to the alveoli, where they encounter warm, moist, nutrient-rich conditions that can promote pathogen development and absorption into the blood stream. Many multi-celled parasites are in the ingestible size range.

The occurrence of microbial or other pathogenic organisms in soils (and therefore in dusts produced from the soils) is strongly influenced by the physical and chemical characteristics of the soil, along with climate, vegetation, and the extent of activities of humans, wildlife, or other organisms. Pathogens that form spores (such as *B. Anthracis*, and *C. Immitis*) have the ability to survive extended dry periods in the soils. Pathogens that lay eggs or that form cysts or oocysts (including worms and protozoa such as *Giardia lamblia*) can also survive for extended periods of time in soil, with the duration enhanced by, but not a requirement of, elevated soil moisture.

Important physical and chemical characteristics of soil that influence the species of pathogens present include pH, water content, and the presence or absence of abundant organic matter, clays, or soluble salts. *C. Immitis* fungus is endemic in much of the arid U.S. southwest and in parts of South America where climates are seasonally dry and winters are short. It competes successfully against other microbes in soils that are alkaline, and that have abundant pore spaces, low clay and organic matter contents, high salinity, abundant evaporative salts, and, possibly high boron contents (Bultman et al. 2005). The boron, tied up in soluble borate salts, may act as a microbicide that inhibits bacterial growth.

Fluid compositions and chemical environments present along the exposure route

The various body fluids are largely aqueous electrolyte solutions with a complex but variable array of organic components such as amino acids, sugars, other organic acids, low- to high-molecular weight proteins, lipids, and enzymes. As indicated in the exposure route section and summarized in Table 2 and Figures 5 and 6, an earth material to which the body is exposed can encounter substantially different chemical environments and fluid compositions between and along the various exposure routes. Several fluid types encountered along ingestion and dermal exposure routes (saliva, gastric fluids, and sweat) can also vary substantially in pH and electrolyte amounts and proportions as a function of their secretion rates (Thaysen et al. 1954; Freudenrich 1998), thereby adding further complexity to the chemical conditions potentially encountered along these exposure routes.

Geochemists familiar with fluid-mineral reactions will immediately recognize that these differences in chemical composition create a strong likelihood that a particular earth material and any contained or adsorbed toxicants may have quite different chemical responses in the body depending upon the exposure route (Plumlee and Ziegler 2006). For example, most minerals or other phases are likely to be more soluble and more readily dissolved in the acid conditions of the stomach than in the near-neutral pH fluids lining the lungs. Differences in electrolyte compositions also influence the solubilities of some solid phases between and along the different exposure routes. An obvious example is the substantially greater stability

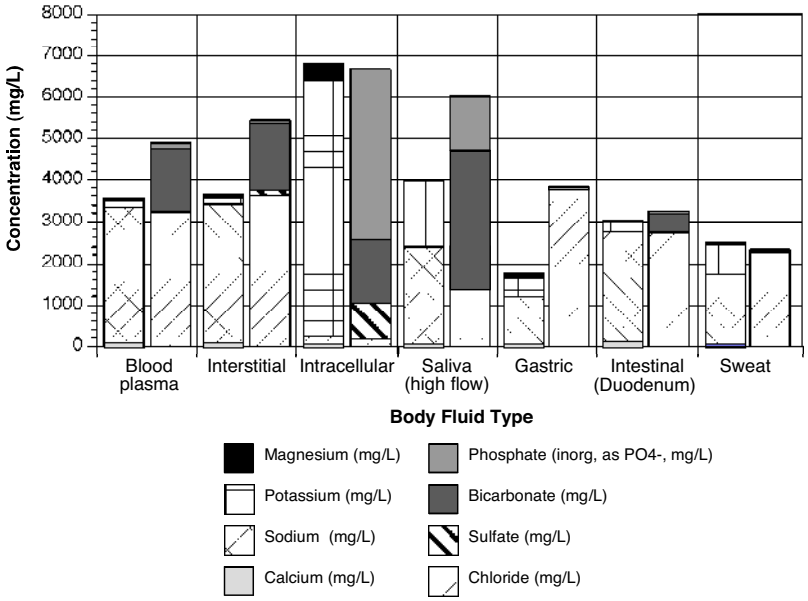

Figure 5. Concentrations of the major inorganic electrolyte species can vary substantially between different body fluid types. These variations play an important role in the relative solubility of a variety of minerals and earth material components along the different exposure routes. Modified from Plumlee and Ziegler (2006).

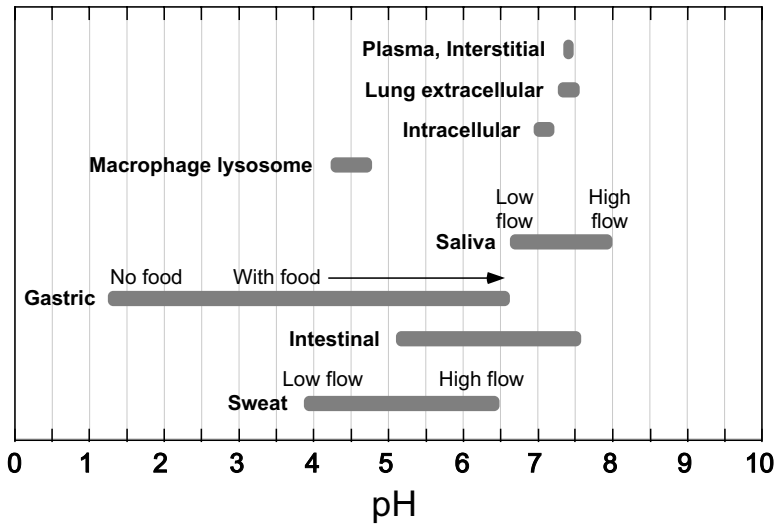

Figure 6. The ideal pH range for proper physiological function of most of the body is a narrow range around 7.4, and so the body employs a variety of physiological mechanisms to maintain the pH of the plasma and interstitial fluids within this range. However, other body fluids are maintained to different pH values depending upon physiological function, such as the gastric fluids, intracellular fluids, and macrophage lysosomal fluids. The pH of gastric fluids, sweat, and saliva are known to vary as a function of secretion rate and, in the case of the gastric foods, with or without the presence of food.

of carbonate minerals in the near-neutral, bicarbonate-rich lung and interstitial fluids than in the acidic, bicarbonate-poor stomach acids. Differences in phosphate levels between the different fluids likely also play a role in the relative solubility of various phosphate minerals; for example, lead phosphates would be expected to be substantially less soluble in the lung, interstitial, and macrophage lysosomal fluids than in the phosphate-poor gastric fluids.

The chemical species dissolved or desorbed from earth materials can also undergo a variety of chemical transformations in the body, such as chelation with inorganic or organic ligands, changes in oxidation/reduction (redox) state, sorption onto other less soluble phases, and re-precipitation as new phases that are more stable under the ambient chemical conditions (Plumlee and Ziegler 2006). Geochemical concepts developed to explain element mobility in the environment (Smith and Huyck 1999; Smith 2006) are also useful to help understand these chemical transformations and element mobility along the different exposure routes in the body. The nature and extent of these chemical transformations can differ extensively between the exposure routes, and also vary sequentially along an exposure route. One obvious example is the increase in pH encountered during the transition from the stomach to the intestines, which likely leads to the precipitation of secondary phases such as carbonates or oxyhydroxides in the intestine. Sorption onto solid particles in the more alkaline conditions of the intestinal tract may further reduce the mobility in and absorption by the body of metals such as lead whose sorption characteristics are strongly enhanced at near-neutral pH. In contrast, the pH increase from the stomach to the intestines may enhance the mobility of some metals that are effectively chelated by organic ligands, which become deprotonated and therefore more available for chelation; it may also enhance the mobility of potentially toxic oxyanion species such as arsenate, selenate, chromate, and tungstate that desorb as the pH increases. Another example is the increase in acidity and decrease in overall redox state as particles insoluble in the near-neutral alveolar fluids are phagocytized by the alveolar macrophages, which can enhance the solubilization of mineral particles such as oxides or oxyhydroxides. However, this enhanced solubilization may be counterbalanced by other chemical conditions within the macrophages. For example, even though uranium oxide particles are noted to dissolve in rat macrophage phagolysosomal fluids, the released uranium most likely reprecipitates within the macrophages as a secondary phosphate phase due to the high levels of intracellular phosphate (Kreyling et al. 1992).

Redox environment. By expending energy, the body can drive or exploit myriad organic and bioinorganic chemical reactions to maintain proper physiologic function in an oxygenated environment with which it is well out of chemical equilibrium. Nowhere is this better illustrated than by the multiple oxidation-reduction reactions that the body manipulates. There are a number of different redox couples or systems that are thought to variably influence the redox environments that are encountered by earth materials along the various exposure routes. Important examples include oxidized/reduced glutathione (GSSG/GSH), ascorbic acid (which at plasma pH includes ascorbate, ascorbyl radical, and dehydroascorbic acid), cysteine-cystine, thioredoxin, nicotinamide adenine dinucleotide phosphate ($NADP^+$/NADPH), and pyruvate-lactate (Buettner 1993; Shafer and Buettner 2001, 2003). Multiple couples (many of which are interlinked chemically) may be active in a given region of the body, with the overall redox environment and Eh in that region due to the combined action of the different couples present (Shafer and Buettner 2001, 2003). The relative importance of each redox couple in each environment is a function of its electrode potential (Fig. 7) and the reservoir size for the pair in the particular body fluid (Shafer and Buettner 2001, 2003). Most literature sources indicate that the overall Eh of the plasma is generally poised in the area of −100 millivolts, due to the combined action of redox couples or systems such as cysteine-cystine, dehydroascorbate-ascorbate and others. In contrast, the intracellular Eh is likely dominated by the glutathione GSSG/GSH couple, due to its substantially greater abundance in the intracellular fluids than the other couples. However, the NADP+/NADPH couple is also present and serves to recycle the GSSG/GSH couple due to its overall lower Eh (Fig. 7). As a result, the intracellular redox

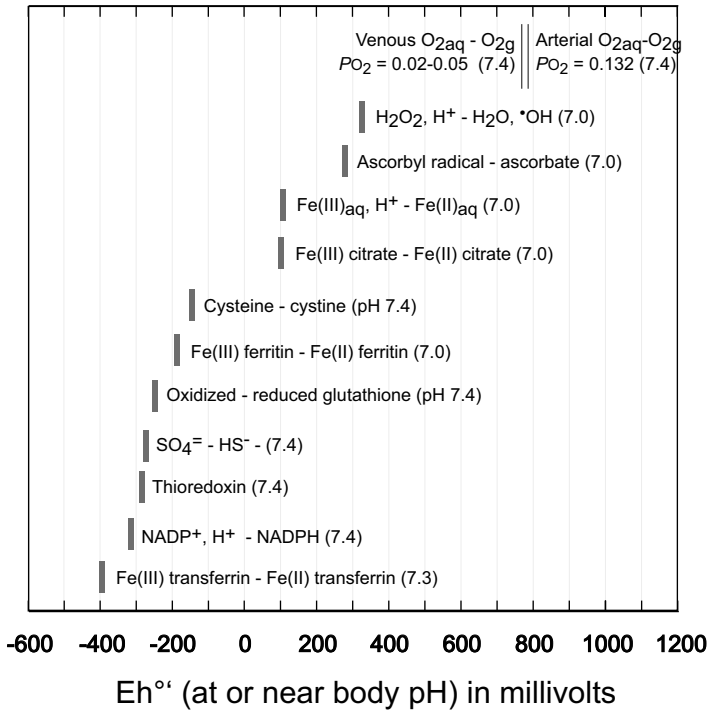

Figure 7. Although it is well-known in the environmental chemistry community that Eh measurements are fraught with uncertainties (poisoning of the electrode, uncertainty in which of many possible redox couples are actually controlling the measurement, etc.), Eh is commonly used in the biochemical literature to compare the relative oxidation-reduction potential of various biologically active redox couples. This figure plots the Eh for a number of different organic and metal-organic redox couples that are known to occur within the body, compared to inorganic ferrous-ferric iron, sulfate-sulfide, dissolved oxygen, and reactive oxygen species couples (data from: Buettner 1993; Shafer and Buettner 2001, 2003, and the thermodynamic database contained in the Geochemists Workbench chemical speciation and reaction-path modeling program; Bethke 1996). Redox couples with higher Eh values would tend to oxidize couples with a lower redox potential. However, as noted by Schoonen et al. (2006, this volume), the relative Eh for each of the redox couples shown on the plot is for equal activities of the two species in solution; hence, particularly for the reactive oxygen species couples, if one of the pair occurs in the body at substantially lower concentrations than the other, this would shift the relative Eh defined by the couple *in vivo* to a substantially different value.

environment is substantially more reduced than that of the plasma, with values closer to −200 to the −240 millivolts of the glutathione couple. The GSSG/GSH ratio in the cellular environment is increasingly viewed as a key indicator of cellular redox condition and overall health, with elevated concentrations of the oxidized relative to the reduced form indicative of oxidative stress (Shafer and Buettner 2003).

As shown by Figure 7, the Eh values defined by 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 these various organic redox couples (Plumlee and Ziegler 2003, 2006). Sulfur, iron, and other elements with multiple oxidation states can be similarly out of internal equilibrium and equilibrium with dissolved oxygen in the plasma. Metallothionein proteins and other organic species containing sulfhydril (HS) groups are common in sulfate-

rich plasma or interstitial fluids. Hemoglobin, a protein, similarly contains tightly bound ferrous iron even though the iron atoms in hemoglobin are those with which transported oxygen associates or dissociates (Rhoades and Pflanzer 1992; Taylor and Williams 1995).

Literature sources indicate that the redox environment of the gastric fluids is quite reduced, with H_2S rather than HSO_4^- stable (Keith et al. 2006), and an Eh of around −200 millivolts at pH 1.5-2 (Davis et al. 1992). The predominant redox couples in the stomach are not specified in literature sources encountered to date; however, Sobala et al. (1991) indicate that both ascorbic acid and dehydroascorbic acid are abundant in the gastric fluids, and Keith et al. (2006) indicate that a number of thiol-containing species such as cysteine and glutathione are also present. Oxygen may be present transiently in the stomach from swallowed air; however, as with the plasma, the oxygen is substantially out of redox equilibrium with the active organic redox couples. The overall redox environment of the intestines is likely to also be quite reduced with reduced sulfur forms stable. A number of literature sources on the intestines focus on the glutathione redox couple; for example Assimakopoulos et al. (2006) suggest that oxidative stress, manifested by elevated levels of the oxidized glutathione species, is linked to intestinal obstructive jaundice.

Biosolubility and bioreactivity of earth materials in body fluids

From the geochemist's perspective, the toxicological literature can be interpreted to indicate that geochemical reactions of earth materials with the body's fluids and tissues plays a substantial role in their toxicity and health effects. It is thus useful to classify earth materials based on their relative biosolubility and bioreactivity in the various body fluids and chemical environments encountered *in vivo* (Table 3; see also Plumlee and Ziegler 2003, 2006, and extensive references cited therein).

Biosolubility is the extent to which an earth material dissolves in the body's fluids. *Biodurable* materials are those that are generally bioinsoluble or sparingly biosoluble in body fluids, and so cannot be cleared rapidly by chemical dissolution. *Biopersistence* is the extent to which a substance can resist all chemical, physical, and other physiological clearance mechanisms in the body.

It is important to differentiate thermodynamic versus kinetic drivers of biosolubility. Some minerals are biodurable because there is no thermodynamic driver for them to dissolve, meaning that the composition of the particular body fluid is thermodynamically close to saturation or supersaturated with respect to the mineral. Examples of biodurable minerals with which the plasma electrolyte composition is calculated using chemical speciation modeling to be near or above saturation include calcium phosphate (the primary component of bone), calcium carbonate, quartz, and various sodium-rich zeolites such as mordenite (Plumlee and Ziegler 2003, 2006). In contrast, the plasma, interstitial fluid and intracellular fluid compositions are all substantially undersaturated with a wide variety of biodurable aluminosilicate minerals such as chrysotile, various amphiboles, and other minerals, which suggests that these minerals are biodurable because of kinetic controls on dissolution. As proposed by Jurinski and Rimstidt (2001), chrysotile asbestos fibers are thought to dissolve more rapidly *in vivo* than rod-shaped amphibole asbestos fibers because chrysotile's scroll-like crystal structure causes it to unroll as it dissolves, thereby exposing more surface area and allowing greater dissolution rates.

The *bioaccessibility* of a potential toxicant in a substance is the extent to which it can be extracted from the substance by the body (Hamel et al. 1999). Bioaccessibility is related to biosolubility in that toxicants in biosoluble materials are also bioaccessible. However, earth materials can also contain bioaccessible toxicants that are sorbed or otherwise loosely bound to the surfaces of relatively bioinsoluble particles.

Bioaccessibility is commonly confused in the literature with *bioavailability*, which is defined by toxicologists to be the fraction of an administered dose of a toxicant that is absorbed

Table 3. Cations and metals are typically distributed among a number of different forms in the body, listed here in generally decreasing order of exchangeability. The body's major electrolyte cations occur largely as labile complexes with electrolyte anionic species or carboxylic acids, or as the simple ion. The simple ionic forms of most metals typically are present in very low concentrations due to the abundance of complexing ligands available in the body's fluids. Information from Taylor and Williams (1995), modified from Plumlee and Ziegler (2003, 2006).

Form	Description
Labile inorganic complexes or simple ions	Complexes with electrolytes such as chloride, bicarbonate. May also include rarer metal-hydroxy complexes.
Labile amino acids, amino acid chains (peptides), other organic acids	Complexes with: amino acids (i.e., cysteine, histidine); peptides (chain of two or more amino acids, such as the tri-peptide glutathione); other organic acids (i.e., citrate, lactate, ascorbate). Also mixed ligand complexes involving more than one amino acid and/or other organic acid (i.e., cysteinate-histidinate)
Labile proteins	Metals complexed with lower molecular-weight proteins are typically viewed as relatively exchangeable. Examples include: transferrin (iron); albumin (copper, zinc, other metals).
High molecular weight proteins	Metal complexes with HMW proteins are typically are viewed as relatively inert and non-exchangeable in the body once formed. However, their contained metals can be released if the proteins are degraded through disease or the body's normal protein breakdown and recycling mechanisms. Include, for example: metallothioneins such as ceruloplasmin, a copper protein, and α_2 macroglobulin, a zinc protein; ferritin (an Fe[III]-storage protein); hemoglobin (Fe[II]).
Solids	Cations or metals incorporated in to teeth, bones, cuticles, etc.

via an exposure route, reaches the bloodstream, and is transported in the body to a site of toxicological action. For most potential toxicants contained in earth materials, the following relationship is generally correct:

$$\textit{bioavailability} < \textit{bioaccessibility} < \textit{total concentration}$$

This relationship shows that equating the total concentration of a toxicant in a substance to its bioavailability is the worst-case scenario, and is scientifically valid only in the rare circumstances when the toxicant is completely released from the substance and is in the appropriate chemical form to permit complete absorption by the body (Reeder et al. 2006, this volume; Ruby et al. 1999; Hamel et al. 1999). However, site-specific risk assessments for metals such as lead commonly assume that the metal is 100% bioavailable to allow for a substantial margin of safety (S. Rodenbeck, oral comm. 2006).

A given earth material will likely differ in its biosolubility or toxicant bioaccessibility depending on the exposure route and the particular body fluids with which it is in contact. For example, a broader variety of minerals are biosoluble in the gastrointestinal system than in the respiratory system because the acid conditions of the stomach promote mineral dissolution. Dissolution rates of phagocytized particles in the relatively acidic (pH 4.5) macrophage phagolysosomal fluids are greater than in the near-neutral lung and interstitial fluids (Kreyling and Scheuch 2000).

Casteel et al. (2006), Ruby et al. (1999) and Plumlee and Ziegler (2003, 2006) present a number of examples of how particle mineralogy and morphology influence the biosolubility of earth materials and the bioaccessibility of their potential toxicants. For example, lead tied up in

cerrussite (a very acid-soluble lead carbonate), lead oxides, and lead sorbed onto atmospheric aerosols generated by lead-zinc smelting is substantially more bioaccessible than lead tied up in galena and various lead-phosphate minerals. Very small particles and botryoidal or acicular crystals may be more readily solubilized than coarser, more equant particles of the same mineral due to the greater surface area per unit mass available for reaction with the body's fluids. Particle surface chemistry and other surface phenomena may be quite important in influencing dissolution rates of biodurable minerals (Guthrie 1997).

Bioreactivity is the extent to which an earth material can react with body fluids or tissues to trigger tissue damage or to alter key fluid parameters such as pH, Eh, and/or concentrations of major electrolytes, trace metals, organic species, and redox-active species. Although not specified as such, the toxicological literature seems to describe a continuum between what can be described as *acute bioreactivity* and *chronic bioreactivity* (Plumlee and Ziegler 2006). Acutely bioreactive materials are those that can trigger rapid, substantial changes in fluid chemistry, and possibly cause damage to tissues along the exposure route. Examples include earth materials that produce acids (such as acidic volcanic gases, or acid-generating soluble salts in mine wastes) or those that produce caustic alkalinity (such as cement dust or concrete). In contrast, chronically bioreactive materials are biodurable, and so react primarily at their surfaces with, and slowly release chemicals into, the surrounding fluids and tissues. Examples include crystalline silica or asbestos, which are thought to cause toxicity by generating reactive oxygen species.

Finally, it is important to note that a wide variety of solid earth materials are typically complex mixtures of many different mineral phases, each of which has its own particular biosolubility and bioreactivity characteristics (Fig. 8). For example, the dusts generated by the collapse of the World Trade Center (WTC) in September 2001 were a very complex mixture containing inhalable to respirable particles of acutely bioreactive concrete, various metals or metal alloys (steel, zinc, lead, bismuth), biosoluble gypsum from wallboard, biodurable chrysotile asbestos fibers and crystalline silica, moderately biodurable glass fibers, window glass, and many others (Meeker et al. 2005; Plumlee et al. 2005). As noted by Plumlee and Ziegler (2003, 2006) and Plumlee et al. (2005), the reaction of readily solubilized and reactive WTC components such as concrete particles with lung fluids could theoretically enhance the chemical stability of less readily solubilized components (such as glass fibers and asbestos fibers) from the dusts. The crystalline silica literature notes that the toxicity of crystalline silica dusts is diminished if the dusts contain other aluminosilicate minerals (SSDC 1988). However, we have not encountered in the literature any other appreciable discussions of whether the chemical behavior *in vivo* and resulting toxicity effects of a substance can be modified when that substance is part of a complex multi-substance mixture. Pathogens may also be a part of the complex earth material mixture. Plumlee and Ziegler (2003, 2006) speculated whether borate salts inhaled with *C. Immitis* spores might enhance their viability in the lungs by suppressing macrophage activity. Aside from this speculation, we similarly have not encountered to date in the toxicological or immunological literature any discussion of how chemical reactions of the earth materials hosting the pathogens with the body's fluids might influence the viability of the pathogens *in vivo*.

Immune system mechanisms

The particle clearance mechanisms discussed in an earlier section of this chapter are one small part of the body's complex defense system that helps protect against foreign substances, pathogens, parasites, and mutated cells. A detailed discussion of the immune system is well beyond the expertise of the authors, but can be found in many excellent textbooks on the topic (i.e., Coico et al. 2003). Mechanisms of the immune system that have the greatest influence on earth materials and their contained toxicants include:

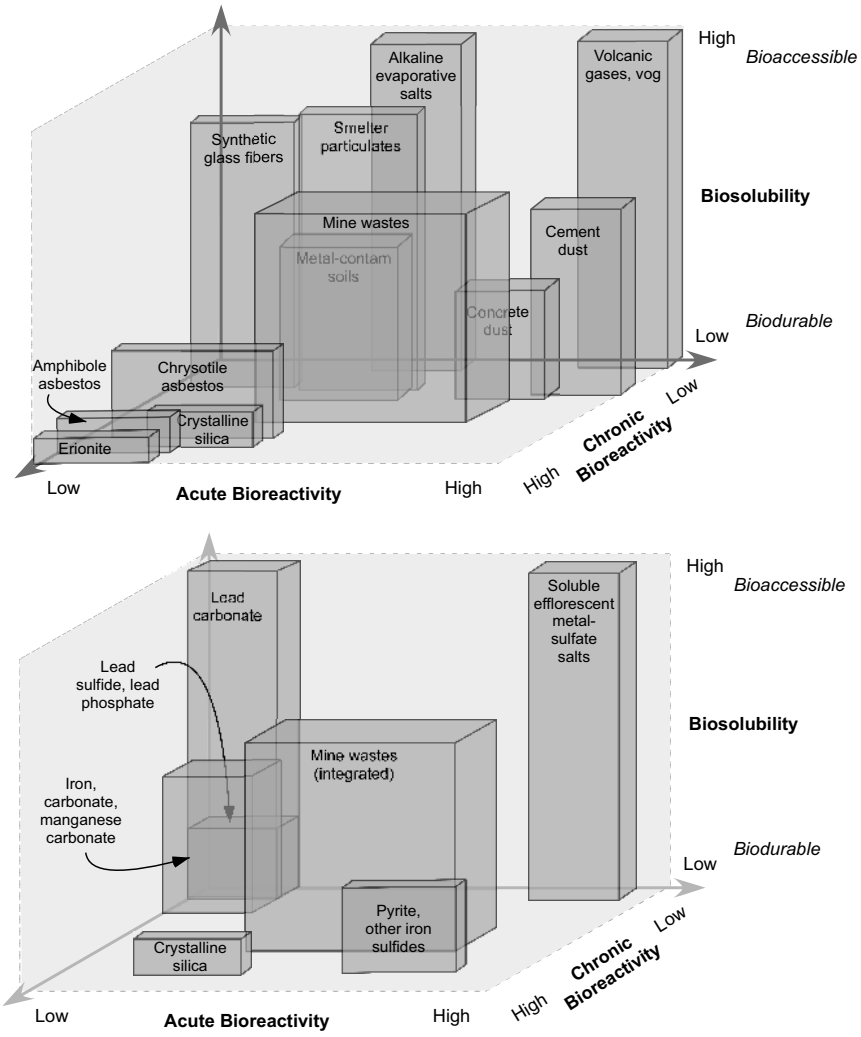

Figure 8. The upper schematic plot shows the inferred biosolubility, chronic bioreactivity, and acute bioreactivity of general classes of earth materials. Many types of earth materials (i.e., mine wastes, volcanic ash, soils) can contain a complex variety of minerals having quite different biosolubilities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

- *Protective barriers.* The skin is one example, but the mucous membranes can also be considered as a physical barrier that helps prevent access of foreign substances and pathogens into the body.
- *Chemical barriers.* These include, for example, the acidic gastric fluids and the digestive enzymes contained in saliva, tears, and gastric fluids. The body's increased production of fluids in the nasal passages and upper respiratory tract in response to the influx of foreign substances is also a chemical defense mechanism that helps dilute chemical impacts of the substance.

- *Microbiological barriers.* The intestines contain a number of different bacteria that compete with pathogens for sustenance, thereby helping to diminish multiplication of pathogens into sufficiently large numbers to trigger illness.
- *Phagocytic activity.* The respiratory macrophages discussed previously one of several types of autonomous phagocytic cells that patrol the body to identify and engulf foreign particles or microbes. The macrophages are in part physical barriers, as they can help isolate foreign substances or pathogens and transport them away from physiologically sensitive areas. They also are chemical barriers in that they can help digest substances with their acidic lysosomal fluids rich in cytotoxic acid proteases and reactive oxygen species. Cytokines (chemical messengers) released from the macrophages can also recruit additional macrophages to the site of particle influx. High burdens of particles and recruited macrophages can lead to increased inflammation of the aveoli, decreased particle clearance, and decreased lung function. Macrophages that are penetrated by sharp particles (Churg 2000; Fattman et al. 2004) or that undergo necrosis (which occurs if they are unsuccessful in engulfing particles such as fibers, or if the engulfed particles are toxic) can release their cytotoxic chemicals into the surrounding environment, triggering irritation of or toxicity to surrounding tissues that can in turn lead to diseases such pulmonary fibroses.

Physiological processes by which potential toxicants from earth materials are absorbed, distributed, metabolized, and/or eliminated by the body (ADME)

There are many processes by which toxicants are absorbed, modified, stored, and eliminated; for detailed descriptions, interested readers are referred to toxicology overview volumes and texts such as Sullivan and Krieger (2001), and Klassen (2001). The brief and greatly simplified discussion here is intended to illustrate how the chemical form of a potential toxicant as released from an earth material plays a role in its ADME. Examples for specific metals and other toxicants contained in earth materials are given in Reeder et al. (2006, this volume) and Plumlee and Ziegler (2003).

Absorption refers to the passage of a potential toxicant through one of the body's various membranes into the circulatory system. It is generally considered to be the chemical passage of a dissolved substance, but as shown previously, solid particles can also penetrate the linings of the respiratory tract and be taken into the circulatory system. The chemical speciation (Reeder et al. 2006, this volume) of a potentially toxic substance as it is derived from an earth material, as well as any chemical transformations that the substance undergoes through reactions with the body's fluids (including dissolution, chelation, precipitation, changes in redox state), strongly influence its absorption.

There are a wide variety of organic ligands in the body that are available to chelate (complex) metals and cations released from earth materials, including (listed in decreasing order of lability; Table 3): simple ions or labile inorganic complexes; labile complexes with amino acids, amino acid chains (peptides), other organic acids (i.e., carboxylic acids such as ascorbate, citrate, lactate), or mixed ligands; labile low-molecular-weight proteins (such as transferrin); generally non-labile, high-molecular-weight proteins (such as ferritin, hemoglobin, metallothioneins); and solids (bones, teeth). Complexation can diminish a metal's tendency to sorb onto solids or precipitate as a solid, both of which can inhibit absorption. Most literature sources suggest that the chemical species that are most readily absorbed through the body's membranes into the circulatory system and that pass most readily pass through the cell membranes, are those with net-neutral charge (Taylor and Williams 1998) or those that mimic the chemical behavior of other physiologically important species. An example of the latter is hexavalent chromium (Cr[VI]), which, similar to sulfate and phosphate species, can be transported via facilitated diffusion through nonspecific anion channels.

Changes in redox state as a metal is delivered from the earth material along the exposure route can also influence its dissolution from the earth material and its absorption by the body. Redox processes can enhance the solubility of solids, such as the enhanced dissolution of metal oxide particles by reduction of their contained metals at the particle surface via ascorbate or other organic reductants. In the case of absorption, changes in redox state are particularly important if the resulting redox form is more or less readily complexed, is present in a more absorbable form, or has diminished solubility. The relative $Eh^{\circ\prime}$ (at or near the appropriate ambient pH) of various redox couples, such as shown in Figure 7, may provide some idea of the relative redox stability of a particular metal or metal particle relative to the body's various redox systems. However, the extent and rates of particular of redox reactions may depend on a variety of factors such as the ambient chemical environment, the availability of the species constituting the dominant redox system(s) for the metal in the particular body fluid, and kinetics of redox reactions. For example, Cr(VI) is more readily reduced under the acid conditions of the gastric fluids than in the near-neutral pH lung fluids, interstitial fluids, and plasma (ATSDR 2000). Cr(III) produced in the stomach by Cr(VI) reduction then most likely precipitates out in the intestines and is not absorbed into the bloodstream. In the lungs, Cr(VI) is relatively soluble in the lung fluids, and is readily absorbed into the bloodstream. It can also persist in the plasma in spite of the many abundant organic reducing agents, and can then cross cell barriers, where it is more readily reduced in the more reducing, glutathione-rich intracellular environment.

Distribution refers to the transport of the potentially toxic substance by the circulatory system to various organs or tissues. As with absorption, transport within the body to specific target organs or tissues may be restricted by various membrane barriers such as the blood-brain barrier. Toxicant forms that are most readily exchangeable (Table 3) are also most readily available for distribution to the tissues and organs (Sipes and Badger 2001).

Metabolism refers to the biochemical transformations that potential toxicants undergo within the tissues or organs, which may include binding, storage, generation of toxic metabolites (also called toxic bioactivation), and detoxification of the toxicant and/or its metabolites (Sipes and Badger 2001). Important storage areas include adipose tissue for lipohilic substances, and the bones for fluoride, lead, and strontium. The liver is one of the primary organs in which generation of toxic metabolites and detoxification occurs, primarily due to its high content of enzymes used to catalyze biotransformation. However, the kidneys, lungs, stomach, intestine, gonads, and skin can also host a variety of metabolic transformations.

Elimination is the mechanism by which the body rids itself of toxicants, toxic metabolites, and metabolic wastes. Although the primary excretion pathway is renal, some materials may be excreted in the bile, feces, milk of lactating women, respired air, sweat, hair, nails, and saliva.

Extent to which earth materials or their contained toxicants can generate reactive oxygen species

Reactive oxygen species (ROS) generated by earth materials or by a variety metals released from earth materials *in vivo* can be an important source of toxicity. Discussed in detail by Schoonen et al. (2006, this volume), ROS are intermediate oxidation state species that are formed by the incomplete oxidation of molecular oxygen and a variety of other redox-sensitive organic species (such as ascorbate) present in the body. Examples of ROS include superoxide ($O_2^{\bullet -}{}_{aq}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}OH_{aq}$). Intermediate oxidation state forms of organic species such as ascorbyl radical can also form. The body exploits some ROS to its benefit; for example, the macrophages can generate ROS to help attack engulfed particles and microbes. However, ROS are implicated in a broad variety of toxicity effects such as oxidative damage of lipids, proteins, and DNA, which can in turn lead to a wide variety of diseases such as cancer (Kawanishi 1995).

Earth materials may generate ROS by a variety of mechanisms (Fubini and Areán 1999; Aust et al. 2002; Schoonen et al. 2006, this volume). A variety of metals are noted in the literature to participate in redox reactions that produce ROS, including iron, manganese, copper, chromium, nickel, titanium, and others. The reactions through which metals can generate ROS are noted to occur either in solution (i.e., if the metals are dissolved from earth materials) or if the metals are structurally bound to particle surfaces. In fact, reaction rates involving structurally bound metals can be considerably faster than those involving dissolved metals, because coordination of the metals with anionic species on the particle surface shift the metal redox couples to effectively lower Eh values, making them more effective electron donors (Schoonen et al. 2006, this volume).

A variety of studies have demonstrated that pyrite (iron disulfide), nickel sulfide, and other metal sulfides can be highly effective at production of hydrogen peroxide and ROS, and breakdown of RNA (Borda et al. 2004; Cohn et al. 2006; Schoonen et al. 2006, this volume). Iron sulfides in coal are increasingly suspect as a contributor to coal-workers' pneumoconiosis, due to the generation of ROS by sulfide particles or by iron released from the sulfide particles or sulfide oxidation products in the coal (Huang et al. 1998 2005). Oxidation of iron sulfides *in vivo* may also generate acid that could be a source of irritation (Plumlee and Ziegler 2006).

Grinding-induced surface structural defects, particularly on freshly ground mineral particles, can generate a variety of ROS (Fubini and Areán 1999). Although crystalline silica is best known for this effect, a variety of other minerals have also been investigated, such as metal oxides, sulfides, asbestos, and zeolites (see references in Schoonen et al. 2006, this volume).

ROS can also be generated when the body's clearance mechanisms fail to clear inert particles from the lungs. Alveolar macrophages activated by foreign particles produce and release into the surrounding alveolar environment a variety of ROS and chemicals that recruit additional macrophages to the site. Macrophages that fail to clear particles also release a variety of cytotoxic chemicals into their surrounding environment. All of these activities contribute to inflammation and can, in the case of biodurable or biopersistent particles, lead to long-term opportunities for DNA damage and resulting toxicity

Susceptibility of the exposed individual

Many confounding factors influence an individual's susceptibility to toxicants contained in or released from earth materials. These can include genetics, age, gender, socioeconomic status, nutritional status, general health status, and personal habits such as smoking.

Genetics, age, and gender. It is increasingly recognized, but in some specific cases debated, that genetics and age can play an important role in an individual's response to environmental and workplace toxicants. For example, genetic factors may influence the susceptibility of individuals to heavy metals by affecting production of enzymes involved in the synthesis and cycling of glutathione, metallothioneins, and other sulfhydril compounds used by the body to help detoxify heavy metals (Gochfeld 1997). Immature and elderly individuals generally appear to be more susceptible to metal toxicity than mature adults. For example, absorption of lead is substantially greater in the intestines of immature organisms than in adult organisms, and the vulnerability of their immature organs to metal toxicity may be substantially greater as well, particularly with respect to neurotoxins that can affect the developing neurosystem (Gochfeld 1997). Production of metallothioneins and other metal detoxifiers may also diminish with age. The role of gender has been shown to be a potential link to disease, particularly as it relates to differences in practices between males and females of a population (that would presumably lead to differences in exposure to a particular workplace or environmental toxicant); possible physiological differences in metal metabolism between males and females are discussed briefly by Gochfeld (1997).

In a study of a population exposed to elevated arsenic in drinking water, Meza et al. (2006)

found that small differences in a particular gene could be correlated with differences in the arsenic metabolites found in the urine of children, but not adults. This indicates that different individuals might metabolize and detoxify arsenic in different manners, and further suggests that the differences in arsenic metabolism may also be influenced by age.

A scan of the medical literature and internet discussion boards quickly encounters lengthy discussions of the possible links between mercury exposure and genetic susceptibility to autism. One published hypothesis is that children with autism may have a genetically based, diminished ability to eliminate mercury from their bodies that results from exposure to mercury *in utero* or as infants. However, this is the focus of continuing debate (Stehr-Green et al. 2003; Mutter et al. 2005). As these discussions are focused on the exposures to mercury contained in a particular vaccine, their implications for potential exposures to mercury contained in earth materials remain to be determined.

Dogan et al. (2006) studied exposures to erionite (a fibrous zeolite associated with asbestos-related disease) in several Turkish villages with extremely high rates of mesothelioma cancer. Because the mesothelioma occurrences are noted to occur only in specific houses, the original hypothesis was that individuals in these households were exposed to a more carcinogenic variety of the erionite. However, mineralogical studies indicated no significant differences in the erionite between affected and unaffected households, and pedigree studies indicated that malignant mesothelioma was prevalent in some families and not others. Dogan et al. (2006) interpreted these results to indicate that mesothelioma development occurs in genetically predisposed individuals, and that genetics therefore plays a direct role in mineral fiber carcinogenesis.

Socioeconomic, health, and nutritional status. The overall health and nutritional status of an individual is thought to influence susceptibility to toxicants (WHO 1996; Gochfeld 1997). For example, nutritional deficiencies of calcium, iron, proteins, and phosphate can enhance absorption of cadmium and lead from the intestine. Some diseases of organs such as the kidneys and liver that are involved with metal metabolism can enhance the body's susceptibility to metal toxicity. Conditions such as chronic asthma or others that diminish airflow to the alveoli may actually diminish particle deposition and resulting toxicity in the lungs. Socioeconomic status can influence overall health and nutritional status, and may influence the extent of environmental exposures to toxicants.

Smoking. Smoking can have several important influences on an individual's susceptibility to toxicants. Cigarette smoke contains a variety of potentially toxic metals (such as chromium), organics, and particulates, and is therefore a well-known trigger of disease in its own right. Nicotine can suppress the concentration of reduced glutathione in the liver, leading to diminished metal detoxification. Smokers 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). Inhaled mineral particles such asbestos may also interact with the chemicals in cigarette smoke to enhance toxicity (Fattman et al. 2004); for example, asbestos fibers that have sorbed toxic organic chemicals from cigarette smoke may carry these toxicants to the tissues or lymph system, thereby allowing prolonged contact of the absorbed toxicants with the surrounding cells.

Summary—an overview of how earth materials can cause toxicity

Some earth materials (for example, asbestos, crystalline silica, and oxides of some metals such as chrome) are toxic because they are not readily cleared by the body, and thereby can persist and/or accumulate at the exposure site or elsewhere in the body. Toxic effects for these types of substance in part result from the body's failed attempts to detoxify and/or excrete them. Macrophages that unsuccessfully engulf insoluble particles can die, releasing their contained cellular toxins to the surrounding cells, leading to tissue death and scar tissue buildup

(fibrosis). Inflammation and other immune responses to solid earth materials may also play a role in disease; for example, chronic beryllium disease is a cell-mediated immune response that triggers lung disease (Goyer and Clarkson 2001). In addition, biodurable substances may exhibit chronic bioreactivity that leads to adverse effects. For example, reactions of chemicals (such as iron) contained in biodurable substances may produce free radicals and other ROS, which can in turn compromise cell integrity or lead to long-term accumulative damage to cellular DNA, and potential diseases such as cancer.

The toxicities of substances that encounter the body in bioaccessible form (those that are readily released from the earth materials into the body fluids) depend upon the exposure route, the dose, the chemical form of the substance at exposure, and the processes that chemically transform the substance during absorption, transport, and metabolism. There are myriad ways in which toxicants released from earth materials can cause chronic and/or acute toxicity. These can include, for example: generation of reactive oxygen species; interference with the body's antioxidant processes and mechanisms; impairment of cellular function; replacing essential elements in key physiological chemicals (such as cadmium replacing calcium in bone); and many others.

Earth materials can also generate toxicity if they are acutely bioreactive, whereby they react chemically with the body's fluids and tissues to the extent that they trigger extensive changes in body fluid composition and tissue damage. The tissue damage may of itself be problematic if it is sufficiently extensive to interfere with physiological function. Damage to protective tissues such as the skin may also provide an entrance point for pathogens. Examples of acutely bioreactive earth materials include: liquids such as acids (i.e., acid gas condensates from volcanoes or automobile exhaust) or alkalis (i.e., liquid sodium hydroxide drain cleaner); gases such as acid gases produced by volcanoes and fossil fuel combustion; alkaline solids such as cement or concrete dust; and acid-generating solids such as soluble metal-acid sulfate salts formed by the evaporation of acid-mine drainage.

Soils, dusts, and other earth materials can host pathogens, and can serve as carriers for the pathogens into the body (e.g., Bultman et al. 2005). Relatively little work appears to have done that investigates whether the form of the earth material with which a particular pathogen is associated may influence the pathogen's ability to persist and thrive *in vivo*.

INTEGRATING EARTH AND HEALTH SCIENCE METHODS TO ASSESS THE HEALTH EFFECTS OF EARTH MATERIALS

A spectrum of earth and health science analytical methods (Table 4) have been or can be applied collaboratively to help understand the toxicological geochemistry and health effects of earth materials. The earth science methods include a wide range of laboratory, computer, and field techniques commonly used to:

- Characterize the physical and chemical characteristics, materials makeup, geochemical speciation, and geochemical reactivity of earth materials;
- Map spatial variations in the occurrence, chemical composition, and other characteristics of earth materials;
- Model the chemical speciation and chemical evolution of water-based fluids in response to mineral-fluid interactions or other chemical drivers;
- Fingerprint sources of potential toxicants or other materials that are derived from earth materials and found in the environment or human body.

The health science methods range from the global, national, or regional scale examined with epidemiological databases and biomonitoring studies, down to the microscopic scale

Table 4. Earth and health science methods that have been or may be used to help understand the health effects of a variety of earth materials. In general, we have tried to provide references for each that illustrate use of the method in a health-related case study. General references are cited in the case of methods for which we are unaware of health-related case studies. "Source" samples are those of soils, dusts, or other earth materials that are potential sources of exposure and toxicity to humans or other organisms.

Method	Use(s) and notes	Studies
Geologic maps and mineral occurrence databases	Show the occurrences (or distribution of rock types that may have potential to host occurrences) of asbestos, fibrous zeolites, or other potentially toxic earth materials. Can be linked to epidemiological studies of disease occurrence tied to geology-sourced toxicants such as asbestos.	**Naturally occurring asbestos:** Churchill and Hill (2000); Van Gosen (2005, 2006a,b); Pan et al. (2005); Schenker et al. (2006); Brodkin et al. (2006).
Geochemistry surveys and geospatial databases for soil, stream sediment, water quality, plants, etc.	Map the distribution of chemical elements in soils stream sediments, waters, plants, and other media. Useful for mapping regional variations and local anomalies away from baseline trends.	**Natural Soils:** Garrett (2005) **Urban soils:** Mielke (1999), Mielke et al. (2004, 2006) **Arsenic in ground water:** Ryker (2001)
Remote sensing techniques	Use plane- or satellite-based sensors to remotely map the distribution and characterize the makeup of earth material sources in the environment.	**Naturally occurring asbestos:** Swayze et al. (2004) **World Trade Center dusts:** Clark et al. (2005)
Phase contrast microscopy (PCM), polarized light microscopy (PLM)	Use transmitted light microscope to identify phases present (based on optical properties), and particle morphology. Sample types include bulk source samples, samples taken from air filters, tissue samples, others	**Asbestos:** Millette (2006); Roggli and Coin (2004); Dodson (2006).
X-Ray Diffraction (XRD)	Identifies crystalline phases present in bulk source samples, using qualitative to semi-quantitative data reduction routines. Can readily identify nearly all major mineral components of multi-phase mixtures, but some minerals may have interferences from other minerals that preclude their certain identification. Can detect minerals present in mixtures in amounts generally greater than 1-2 weight %.	**Asbestos:** Meeker et al. (2003) **World Trade Center dusts:** Meeker et al. (2005)
Scanning electron microscopy (SEM)	Determines identity, morphology, and chemical composition of solid phases down to less than 1 micron in size based on semi-quantitative energy-dispersive x-ray analysis. Also used to map microscopic distribution of chemical elements in a sample. Sample types include bulk source samples, dust samples from air filters, tissue samples, plants, others.	**Asbestos:** Meeker et al. (2003); Roggli and Coin (2004); Millette (2006); Dodson (2006) **World Trade Center dusts:** Meeker et al. (2005) **Depleted uranium fragments in tissue samples:** Todorov et al. (in press)
Electron probe microanalysis (EPMA)	Provides quantitative and qualitative chemical composition data on spots within mineral grains or other solid phases. Requires polished section or grain mount for optimum results. Mostly for source samples.	**World Trade Center dusts:** Meeker et al. (2005) **Libby asbestos:** Meeker et al, (2003)

(table continued on next page)

Table 4. *(continued)*

Method	Use(s) and notes	Studies
Transmission electron microscopy (TEM)	Integrates electron diffraction and SEM capabilities at a microscopic, single-crystal scale. Sample types include small amounts of bulk source samples, dust samples from air filters.	**Asbestos:** Millette (2006); Dodson (2006); Roggli and Coin (2004)
Atomic force microscopy (AFM) and Vertical Scanning Interferometry (VSI)	Mapping of and measurement of changes in microscopic surface topography of solid samples. Can be used in mineral dissolution studies (such as physiologically-based extraction tests) to measure changes in surface topography that occur in response to mineral-fluid interactions.	**General:** Cama et al. (2005); Arvidson et al.. (2003)
X-ray absorption spectroscopy (XAS) and Extended X-ray absorption fine structure (EXAFS) spectroscopy	Measurement of microscopic variations in the chemical form (speciation) and distribution of potentially toxic elements in solid samples. Sample types include bulk source materials, dusts, soils, and others. We are not aware of this type of analysis being used yet for foreign earth materials in tissue samples.	**Mine wastes and tailings:** Foster et al. (1998); Kim et al. (2004). **General:** Reeder et al. (this volume)
ICP-MS, ICP-AES, and other analytical chemistry methods	Used to measure the bulk chemical composition of waters, solids, plants, or other earth materials. Solids require acid digestion prior to analysis.	**World Trade Center dusts:** Plumlee et al. (2005) **General:** Taggart (2002); Vutchkov et al. (2005)
Particle sampling methods	Used to obtain appropriately sized (from a physiological perspective) source materials, dust samples, soil samples, etc., for regulatory particle counting, toxicity tests, physiologically-based extraction tests, and other types of health tests.	**General:** Hinds (1999); Baron and Willeki (2001)
In vivo toxicity tests	Measure toxicity effects or exposure indicators as a result of the direct exposure (via appropriate exposure routes) of living animals under controlled laboratory conditions to variable doses of toxicants over time. Uncertainties in how well tests on other species of animals reproduce actual physiological conditions and processes in the human body. Respiratory tests can include instillation (direct placement of materials in trachea of subject animals) or inhalation (subject animals are exposed to an air stream with specific material doses.	**Asbestos, respiratory:** Fattman et al. (2004); Johnson and Mossoman (2001).
In vivo bioaccessibility assessments (uptake monitoring)	Conducted on individuals exposed to potential toxicants to assess the extent to which the toxicants have been absorbed, transported, and metabolized by the body. Can be used to assess whole-body bioaccumulation of the material of concern as well as the particular tissues in which material accumulation takes place	**General:** Plumlee and Ziegler (2006, and references therein) **Lead in soils:** Casteel et al. (2006) **Arsenic in various earth materials:** Buchet et al. (1995)
Pathology analysis of tissues and contained earth materials	Provides a way of directly measuring or assessing toxicant uptake by, interactions with, and toxic effects upon the body, through study of tissue and other samples collected as part of autopsy, biopsy, or other methods such as bronchiolar lavage.	**General:** Centeno et al. (2005a,b) **Asbestos:** See chapters in Roggli et al. (2004); Dodson and Hammar (2006). **Depleted uranium:** Todorov et al. (in press)

(table continued on next page)

Table 4. *(continued)*

Method	Use(s) and notes	Studies
In vitro physiologically-based bioaccessibility or biodurability tests	Used to analyze and measure rates of chemical reactions between earth materials and various simulated body fluids, including simulated saliva, gastric, intestinal, lung, and alveolar macrophage fluids. The goal 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 tests can vary substantially in: physical design; particle size, shape, and other characteristics of materials tested; fluid compositions; fluid-solid proportions; test duration; and other parameters. Uncertainties include (1) how well the tests reproduce actual (complex and dynamic) 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 toxicity responses *in vivo*.	**General:** Plumlee and Ziegler (2003, 2006) **Lead in soils and mine wastes:** Drexler amd Brattin (2006); Ruby et al. (1999); Hamel et al. (1999); Oomen et al. (2002, 2006). **Asbestos and talc:** Johnson and Mossman (2001); Jurinski and Rimstidt (2001); Werner et al. (1995); Mattson (1994a,b); Eastes et al. (1996, 2000a,b). **World Trade Center dusts:** Plumlee et al. (2005)
In vitro toxicity, uptake, or chemical assay tests	Used to model the effects of toxicants on cultures of living cells or tissues. A carrier medium (such as fetal bovine serum) containing given concentrations, or doses, of a particular toxicant are added to cell cultures (cell lines) approximating the types of cells affected during actual exposure (i.e., lung epithelial cells, alveolar macrophages, etc.) Indicators of toxicity, cellular uptake, or other chemical indicators (such as iron release, cytokine generation, etc.) are then measured after specified periods of time. Uncertainties include how comparable test results are to those of *in vivo* toxicity tests, and how well *in vitro* tests reproduce actual physiological conditions and processes in the human body.	**General:** Plumlee and Zeigler (2006) **Asbestos, respiratory:** Fattman et al. (2004); Johnson and Mossman (2001); Yang et al. (2006). **Lead in soils, ingestion:** Oomen et al. (2003) **Coal fly ash and other materials, respiratory:** Aust et al. (2002)
Biomonitoring studies	Measure potential toxicants and and/or their metabolites in the blood, hair, urine, saliva, tissues and/or other body components of a target population. One goal of such biomonitoring is to assess the proportion of a target population that has been exposed to particular contaminants. Another goal is to establish baseline levels of exposures in a target population.	**General:** NHANES (2006); CDC (2006) **Wildfire:** Wolfe et al. (2004)
Toxicant uptake modeling	EPA's IEUBK (Integrated Exposure Uptake Biokinetic) and similar lead uptake models estimate blood-lead concentrations in children that might result from their exposure to lead from various sources in the environment.	**Lead in soils:** EPA TRW (1999) **Lead in edible soils:** Abrahams et al. (2005)
Epidemiology studies	Correlate disease occurrences and patterns in populations with geospatial data and external parameters such as possible environmental exposures	**Asbestos:** Sporn and Roggli (2004); Lemen (2006); NIOSH WoRLD (2006); Pang et al. (2005); Brodkin et al. (2006); Schenker et al. (2006)

examined by pathology studies of tissue samples. They also include a wide variety of *in vitro* and *in vivo* methods to assess toxicity and other measures of physiological processes.

Rather than discuss each one of these methods in detail, we will instead provide examples of past or future opportunities for earth-health science collaboration to help understand potential health affects of earth materials that contain asbestos and heavy metals such as lead. For more detailed discussions of a number of the methods listed in Table 4, the interested reader is referred to Plumlee and Ziegler (2003, 2006).

ASBESTOS

Asbestos is likely the most recognized and best studied of the earth materials known to cause adverse health effects. Asbestos exposure has been clearly linked to asbestosis, lung cancer, pleural effusions, pleural thickening, pleural plaques, and mesothelioma cancer, and secondary diseases such as cardiovascular problems (Roggli et al. 2004); causal linkages between asbestos exposure and diseases such as gastrointestinal and laryngeal cancers have been proposed in the past but are currently debated (see discussion in Rolston and Oury 2004).

Over the many decades since its health effects were first recognized, asbestos has been the focus of a very large number of studies utilizing many of the earth and health science methodologies listed in Table 4; review papers on the topic, which are themselves too numerous to list here, commonly list many hundreds of references. However, in spite of the decades of study, there is still extensive debate in the mineralogical, toxicological, pathological, and epidemiological literature regarding many aspects of asbestos terminology and toxicity. Two recent textbooks, Roggli et al. (2004) and Dodson and Hammer (2006), provide excellent summaries of the current state of knowledge regarding asbestos and associated health issues. However, these and myriad other literature sources on asbestos also illustrate many areas of continuing debate, remaining data and knowledge gaps, and, as a result, opportunities for future interdisciplinary research.

Lowers and Meeker (2002) presented a revealing summary of the many different ways in which asbestos and related terms have been described and defined in the scientific literature and regulations. In its historical usage, asbestos is a commercially and industrially derived term describing several silicate minerals that form long, very thin mineral fibers, which combine to form fiber bundles commonly showing splayed ends; when crushed, the fiber bundles split into individual fibers that typically show evidence of flexibility (Fig. 9) (Skinner et al. 1988; Van Gosen 2005, 2006a,b). Most current regulatory definitions of asbestos include

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Figure 9 (*on facing page*)**.** A. Hand sample photograph of chrysotile asbestos, locality unkown, showing classic commercial asbestos characteristics. B. Field sample photograph (courtesy of T. Hoefen, S. Vance) of relatively friable masses of fibrous and asbestiform amphibole from Libby, Montana. Many microscopic fibers were easily abraded from the samples during transport to the lab. C. SEM photomicrographs of standards commonly used in asbestos-related toxicity testing (UICC A asbestos chrysotile, NIEHS/RTI K48 asbestos crocidolite, and UICC asbestos amosite). Note that the UICC amosite asbestos sample shows a wide range in aspect ratio and morphology (asbestiform versus blocky to acicular) (photos by H. Lowers, courtesy of T. Ziegler). White scale bars are all 50 microns long. D. SEM photomicrograph of fibrous erionite with fragments of volcanic tuff. Scale bar is 50 μm long (photo by J. Dyken). E. SEM photomicrograph of amphiboles intergrown with vermiculite from Libby, Montana, displaying a substantial range in morphologies (photo by H. Lowers, from Meeker et al. 2003). F. Transmitted light photomicrograph of ferruginous bodies cored by asbestos, found in lung digestate taken from an individual who perished from asbestosis; the individual is thought to have been exposed to asbestos from Libby, Montana at a vermiculite expansion plant. The bodies are interpreted to form as a direct result of the interactions of alveolar macrophages with fibers. Photo reproduced from a color plate in Wright et al. (2001), with permission the American Journal of Respiratory and Critical Care Medicine, American Thoracic Society.

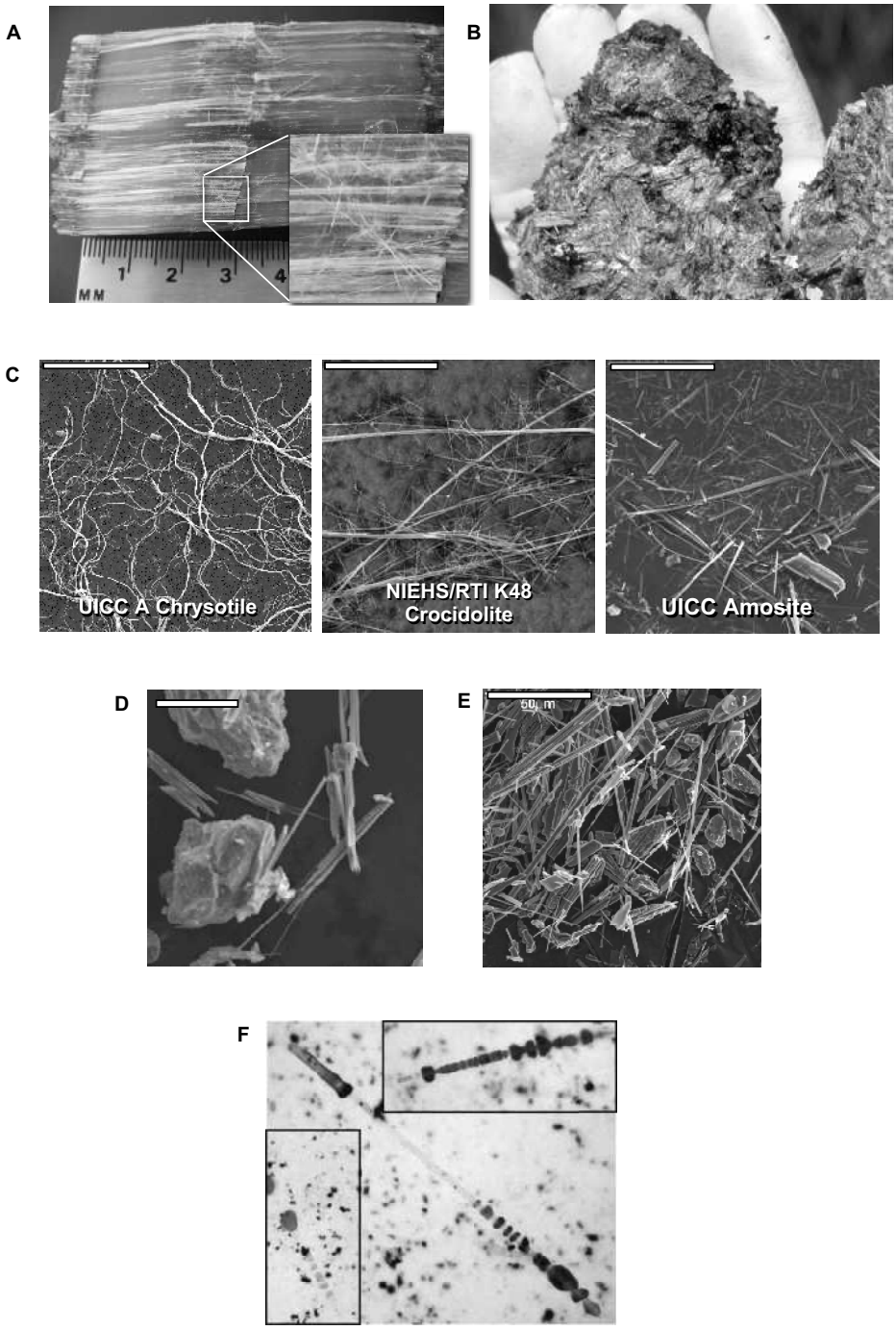

Figure 9. *caption on facing page*

the most commonly used commercial varieties of several different minerals: chrysotile (the asbestiform variety of serpentine), and; the asbestiform varieties of the amphiboles riebeckite (commercially called crocidolite asbestos), cummingtonite-grunerite (commercially called amosite asbestos), anthophyllite (anthophyllite asbestos), actinolite (actinolite asbestos), and tremolite (tremolite asbestos).

Historically, the adverse health impacts of exposure to asbestos-bearing dusts were primarily documented in workers in a variety of trades involved with the mining, processing, or handling of commercial asbestos. Recent attention to high levels of asbestos-related disease via both workplace and environmental exposures to amphibole fibers intergrown with vermiculite mined at Libby, Montana has generated renewed discussions about the specific characteristics of amphibole fibers that influence toxicity (Dearwent et al. 2000; Wylie and Verkouteren 2000; Lybarger et al. 2001; Meeker et al. 2003). It has also led to increased attention to potential health effects resulting from occupational and environmental exposures to dusts generated by mining of mineral deposits that contain asbestos as a natural contaminant (such as Libby), or by natural weathering or human disturbance of certain rock types that contain naturally occurring asbestos (termed NOA) (Renner 2000; Pan et al. 2005; Raloff 2006; Van Gosen 2005, 2006a,b).

Epidemiological studies of worker cohorts exposed to asbestos in the workplace are common in the medical literature, and some epidemiological studies have also been carried out to investigate environmental exposures to commercial asbestos (i.e., see reviews such as Lemen 2006). These epidemiological studies have been used for a variety of applications, such as understanding the prevalence of different types of asbestos disease as a function of exposure and asbestos type. National-scale epidemiological data and derivative maps showing rates of asbestos-related diseases such as asbestosis (Fig. 10) clearly identify areas of elevated disease occurrence in urban areas where workplace exposures were likely greatest, but also indicate other areas of elevated disease incidence where workplace exposures are not as likely.

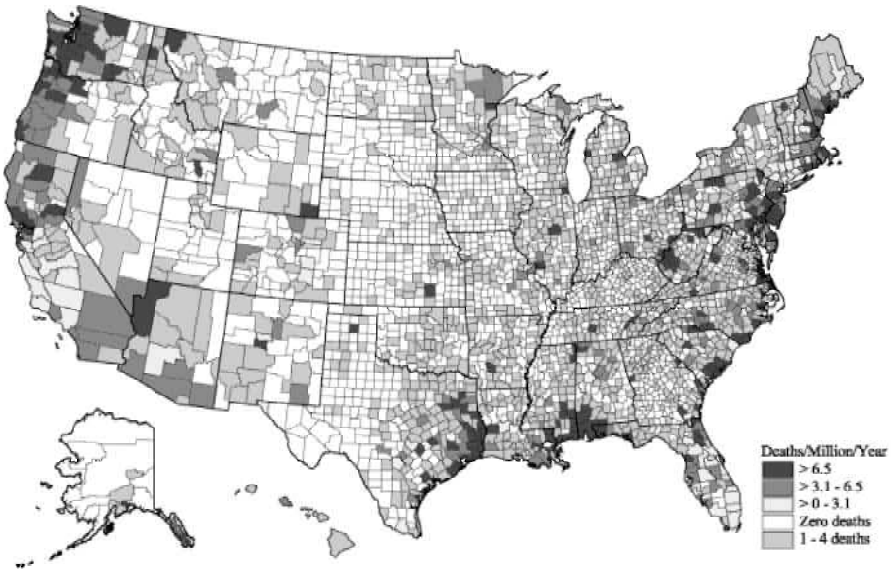

Figure 10. Epidemiological map showing national age-adjusted rates of asbestosis-related mortality by county for U.S. residents age 15 and over, 1970-1999. Reproduced from NIOSH WoRLD (2006).

Pathology studies of tissue samples obtained by autopsy, biopsy, or bronchoalveolar lavage have been used to provide a wide variety of insights into health aspects of asbestos (papers in Roggli et al. 2004; Centeno et al. 2005a,b; Dodson 2006). These include: assessing if an individual has been exposed to asbestos (Fig. 9F), interpreting physiological processes that affect asbestos in the body, diagnosing asbestos-related diseases such as asbestosis or mesothelioma, interpreting if a particular lung cancer case is due to asbestos-related exposure, understanding the type(s) of asbestos to which an individual has been exposed, comparing the asbestos burden in the tissues of exposed and non-exposed populations, and understanding the progression of asbestos-related diseases.

Many different animal-based (*in vivo*) and lab-based (*in vitro*) toxicity tests have contributed substantially to the study and current understanding of asbestos toxicity (see reviews by Johnson and Mossman 2001, and Fattman et al. 2004). *In vivo* inhalation toxicity tests expose subject animals to known concentrations of fibers in an airstream, and *in vivo* implantation toxicity tests involve the direct implantation of fibers in the trachea, pleura, or other tissues of subject animals. The toxicity effects (such as fibrosis, tumor growth, or cell necrosis) after various exposure duration periods are then assessed using pathology studies of the subject animal tissues. In part due to the expense of *in vivo* toxicity testing, a substantial amount of asbestos toxicity testing has shifted in recent years to *in vitro* methods. Cultures of lung epithelial cells, alveolar macrophage cells, or other appropriate target cells are dosed with a suspension of asbestos fibers. Various indications of toxicity are then measured, such as the percent of viable cells remaining at the end of the test (compared to a control line with no added fibers), and the concentrations of various cytokines or other cytoplasmic enzymes produced by the cells. Important uncertainties of these toxicity tests are how well the physiologic processes and endpoints of exposure, dose/response, and toxicity measured in the animal and lab tests can be extrapolated to quantify similar processes and endpoints in humans. One advantage of *in vivo* and *in vitro* toxicity tests is that the test material can be chosen to address specific questions, such as the potential toxicity of short versus long fibers, of amphibole versus chrysotile asbestos, and of asbestos fibers versus cleavage fragments or prismatic or blocky varieties of the same mineral.

In vitro cellular assays also provide useful insights into various physiological processes and cellular function, such as the production of cytokines in response to asbestos exposure, and resulting impacts on surrounding cells *in vitro* and *in vivo* (i.e., Yang et al. 2006).

A variety of *in vitro* acellular tests have been applied to asbestos. A number of studies have examined the generation of reactive oxygen species by iron contained in or released by asbestos (Aust and Lund 1990; Lund and Aust 1992; Fubini and Areán 1999). *In vitro* biodurability tests have been used to examine the chemical reactions of asbestos, cleavage fragments, other mineral particles, and glass fibers with various acids, simulated lung fluids, simulated macrophage lysosomal fluids, and other fluids such as serum-based cell line carrier fluids (Walker 1981; Churg et al. 1989, 1993; Sébastien et al. 1989; Hume and Rimstidt 1992; Werner et al. 1995; van Oss et al. 1999; Jurinski and Rimstidt 2001; Johnson and Mossman 2001; Ziegler et al. 2002). Although such *in vitro* tests cannot reproduce in any detail the complex chemical conditions present in the various regions of the body, they can provide useful comparisons of the relative dissolution rates of different asbestos minerals in proxies for body fluids, and useful insights as to how the fibers might react chemically in the lung or macrophage environment.

Chemical speciation and reaction path modeling (Bethke 1996) has been used to help understand potential solubility constraints on the biodurability of asbestos and other minerals *in vivo*, and to help interpret the results of in vitro biodurability tests (see Wood et al. 2006, and summary and references in Plumlee and Ziegler 2006).

Current views on how asbestos causes toxicity

Although there are still many areas of debate (see next section), studies such as those cited in the previous section have led to a general understanding of how asbestos is toxic. Thin (<0.5 to 1 μm) fibers can flow aerodynamically in to the bronchioles and alveoli, where they lodge by interception. Longer fibers (generally >5-10 μm) cannot be phagocytized by the alveolar macrophages, and so are not as readily cleared as shorter fibers.The biopersistent fibers are not readily cleared by physical breakage or by dissolution in the lung fluids or the more acidic fluids of the macrophage lysosomes, and so can persist *in vivo* for decades. The fibers can also penetrate into the lung tissues and adjacent pleura as a result of the expansion and contraction of the lungs during breathing, and possibly as a result of transportation by the lymph system.

The asbestos fibers are thought to cause toxicity over the long term by a variety of mechanisms. The macrophages release cytokines, which recruit additional macrophages to the site. This influx of macrophages also produces an inflammation response of the local tissues. Macrophages that fail to clear the fibers die and release their cytotoxic chemicals (acid proteases, reactive oxygen species) into the surrounding environment, which can trigger toxicity effects on the surrounding cells. Fibrosis, the buildup of scar tissue, results from the overload of the lung environment by fibers and the lung's failed attempts to clear the fibers.

Several mechanisms are thought to result in carcinogenesis. One of the cytokines released by the alveolar macrophages, TNF-α, is thought to help protect the surrounding cells from short-term toxicity from the fibers, thereby enhancing the fibers' longer-term ability to trigger cellular damage (Yang et al. 2006). The fibers can penetrate the nuclei of the macrophage and lung cells (Churg 2000), where they can physically disrupt the cellular DNA, potentially leading to DNA breaks and mutations. Reactive oxygen species produced by reactions between body fluids and the fibers (and possibly constituents released from the fibers) can also lead to DNA disruption and potential carcinogenesis; iron associated with the asbestos fibers is commonly thought to be an important contributor to the formation of ROS (Aust and Lund 1990; Fubini and Areán 1999).

Aspects of asbestos toxicity that are still under debate

In spite of decades of research into the factors that influence the toxicity of asbestos, there are several areas of continuing debate in the health and mineralogical literature. A few examples (with appropriate references illustrating differences of opinion) are discussed next.

The relative pathogenicity of chrysotile versus amphibole asbestos. A number of epidemiological, toxicological, and pathological studies have generally indicated that amphibole asbestos and erionite are more potent from a carcinogenic standpoint than chrysotile asbestos (i.e., Holland and Smith 2001; Fattman et al. 2004; Sporn and Roggli 2004). Frequently cited pathology studies (e.g., Churg et al. 1984, 1993) found elevated levels of amphibole asbestos fibers (particularly tremolite) in the lung burden of chrysotile miners and workers diagnosed with mesothelioma. These findings were interpreted to indicate that the elevated risk of developing mesothelioma in chrysotile workers was due to natural contamination of the chrysotile ores by tremolite fibers. The amphibole fibers were postulated to have been enriched in the lung burden (and hence associated with increased risk of mesothelioma development) relative to chrysotile fibers as a result of several mechanisms. It is interpreted that amphibole fibers (which tend to be straighter and flow more aerodynamically than the more curly chrysotile fibers) can penetrate deeper into the lungs than the chrysotile. It is also interpreted that amphibole fibers can also penetrate into the surrounding lung tissues and membranes more readily than longer chrysotile fibers, where they can trigger cancers such as mesothelioma.

Results of *in vitro* biodurability tests and other 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 has been interpreted to suggest that amphibole asbestos and

erionite fibers therefore can persist for longer periods of time in the lungs and adjacent tissues than chrysotile, thereby imparting a greater potential to trigger fibrosis and cancer (Sébastien et al. 1989; Churg et al. 1989, 1993; Johnson and Mossman 2001).

However, a variety of recent case studies and reviews (i.e., Suzuki and Yuen 2001, 2002; Lemen 2006; Dodson 2006) cite evidence such as the presence of chrysotile asbestos fibers in mesothelioma tumors, and the occurrence of chrysotile asbestos without amphibole asbestos in the lung burden of some individuals with mesothelioma, to indicate that both chrysotile and amphibole asbestos forms are pathogenic. Asbestos researchers who conclude that chrysotile is as pathogenic as amphibole asbestos (i.e., Lemen 2006) interpret that the more rapid leaching of chrysotile relative to amphiboles in the body is an indication of both its greater degree of bioreactivity *in vivo* (and hence its ability to induce cellular damage), and the presumed increased tendency of the partially leached fibers to break into many shorter fibers that would be available to migrate into adjacent tissues or cells, and potentially trigger toxicity.

A middle ground in the discussion may be the view summarized by Sporn and Roggli (2004): "*…it is clear that sufficient exposure to chrysotile may result in the development of mesothelioma, but in contrast to the commercial amphiboles, low level exposures are not likely to increase risk*."

The potential pathogenicity of short asbestos fibers. A rather traditionally held view in the asbestos toxicological community has been that longer, thinner fibers (>8 μm long, <0.25 μm wide) are more pathogenic than shorter, wider fibers (e.g., Stanton and Wrench 1972; Stanton et al. 1981). The presumption has been that shorter fibers are more rapidly cleared from the lungs than an equivalent number of longer fibers (Dodson 2006).

However, several recent studies of fiber burden in lung and mesothelioma tissues of individuals diagnosed with mesothelioma cancer have found that the majority of the fibers in the tissues were less than 5 microns long, and that chrysotile is a common fiber type (Suzuki and Yuen 2001, 2002; Dodson et al. 2003; Dodson 2006). One interpretation of these results is that shorter chrysotile fibers can also penetrate and migrate to the pleural and peritoneal spaces, and can therefore trigger cancer in these regions.

As noted by Dodson et al. (2003), a workshop on fiber toxicology research needs (summarized by Dement 1990) indicated that much additional information beyond fiber dimension was needed to more fully assess potential fiber toxicity, including surface area, solubility in lung fluid, trace metal and trace organic content, surface charge at physiological pH, and surface reactivity. Dodson et al. (2003) then went on to point out that such information is typically not fully developed in asbestos toxicology studies.

The potential health effects of microscopic, non-commercial amphibole fibers that do not fit all of the compositional or morphological characteristics of regulated asbestos. Several amphibole minerals (as classified mineralogically on the basis of composition) have been noted to occur in a fibrous or asbestiform habit and have been associated with mesothelioma and other asbestos related diseases, but are not specifically listed in asbestos regulations. These include winchite and richterite (e.g., found at Libby, Montana; Meeker et al. 2003) and fluoredenite (e.g., found in Biancavilla, Italy; Giagnfagna et al. 2003). Meeker et al. (2003) also found a range of microscopic morphologies in Libby amphiboles from asbestiform to acicular, prismatic, and blocky. In many Libby samples, acicular prismatic fibers (a number of which are quite straight and show no evidence of flexibility) are commonly observed in SEM images to be parting or cleaving from larger but still microscopic blocky or prismatic amphibole particles. Abundant straight, acicular fibers (including many in Fig. 9E) are also commonly observed by SEM in debris sloughed from friable field samples (Fig. 9B) that had not been subjected to grinding, suggesting that the fibers are single crystals that were somewhat loosely bound within larger masses (G. Meeker, oral comm., 2006). Because the

most clearly asbestiform fibers (as defined for commercial purposes) constitute a relatively small proportion of the total amphibole fibers at Libby (Meeker et al. 2003), this merits the question as to whether the truly asbestiform fibers are the only morphology contributing to the toxicity of the Libby amphiboles. Similar microscopic, non-asbestiform but fibrous or acicular morphologies are rather common in amphiboles from other localities, including in a number of standards used in toxicity testing (Ziegler et al. 2002), suggesting that the same question deserves further consideration beyond Libby.

Cleavage fragments constitute a specific type of broken mineral particle most likely produced primarily by grinding, milling or physical impacts of other human or natural activities on larger crystals. Amphibole cleavage fragments have not been regulated by OSHA since 1992 (see regulatory-focused discussions in NIOSH 1990; OSHA 1992). A recent review paper (Ilgren 2004) argues emphatically for the substantially lower toxicity of cleavage fragments compared to asbestos, citing previous studies and many oral communications. Various toxicity studies cited by Ilgren (2004) have concluded that amphibole cleavage fragments do not pose substantial health risks compared to those of their asbestiform counterparts (e.g., Davis et al. 1991). In contrast, other studies suggest that grinding of silicates (e.g., Fubini and Areán 1999) and "acicular" amphiboles (e.g., Palekar et al. 1979) (which should enhance formation of cleavage fragments) increases their *in vitro* bioreactivity, hemolytic activity, and(or) cytotoxicity. When considered individually and in total, details of these toxicology studies and other studies not cited here indicate perhaps greater uncertainties exist than those conveyed by the Ilgren (2004) review, both in terms of study methodologies and some interpretations regarding the toxicity of cleavage fragments. These uncertainties include, for example: the relative reactivities and toxicities of freshly ground versus aged cleavage fragments; the relative toxicities of predominantly acicular versus predominantly blocky cleavage fragment populations of the same amphibole type; whether differences in sample preparation (e.g. grinding in water versus air) influence surface reactivity and toxicity results; relative dissolution rates of cleavage fragments versus fibers as a function of surface area and composition (Walker 1981, and discussion in Plumlee and Ziegler 2006); and, how major- and trace-element compositional variability may complicate interpretations of toxicity differences between cleavage fragments and asbestiform varieties of the same amphibole.

The potential health risks associated with exposures to dusts containing naturally occurring asbestos. As noted earlier, there is currently substantial interest in understanding the health risks associated with environmental or work-related exposures to naturally occurring asbestos dusts that are released by the natural or human disturbance of asbestos-containing rocks. A recent study (Pan et al. 2005) interpreted epidemiological data for mesothelioma occurrences in the context of geologic maps keyed to the occurrence of potential NOA-bearing ultramafic rocks in California (Fig. 11), and concluded that individuals living on or near ultramafic rock outcrops had a higher risk of developing meothelioma. This study has been the focus of subsequent discussion in the journal (i.e., Brodkin et al. 2006 comment; Schenker et al. 2006 reply). Also, ultramafic rocks are not the only rock type in California known to contain asbestos (see discussions in Van Gosen et al. 2004; Van Gosen 2005, 2006b), so restricting the analysis to only ultramafic rocks may not completely estimate the links between mesothelioma and NOA.

Opportunities for further integrated health and earth science research on asbestos

A review of the asbestos literature from an earth science perspective readily leads to the conclusion that earth science methods and techniques can continue to contribute in many ways to health studies that address the many remaining questions regarding potential health effects of asbestos and other fibrous minerals.

An ongoing effort to map asbestos occurrences and their geologic environments of formation across the nation (Van Gosen et al. 2004; Van Gosen 2005, 2006b) will provide geologic

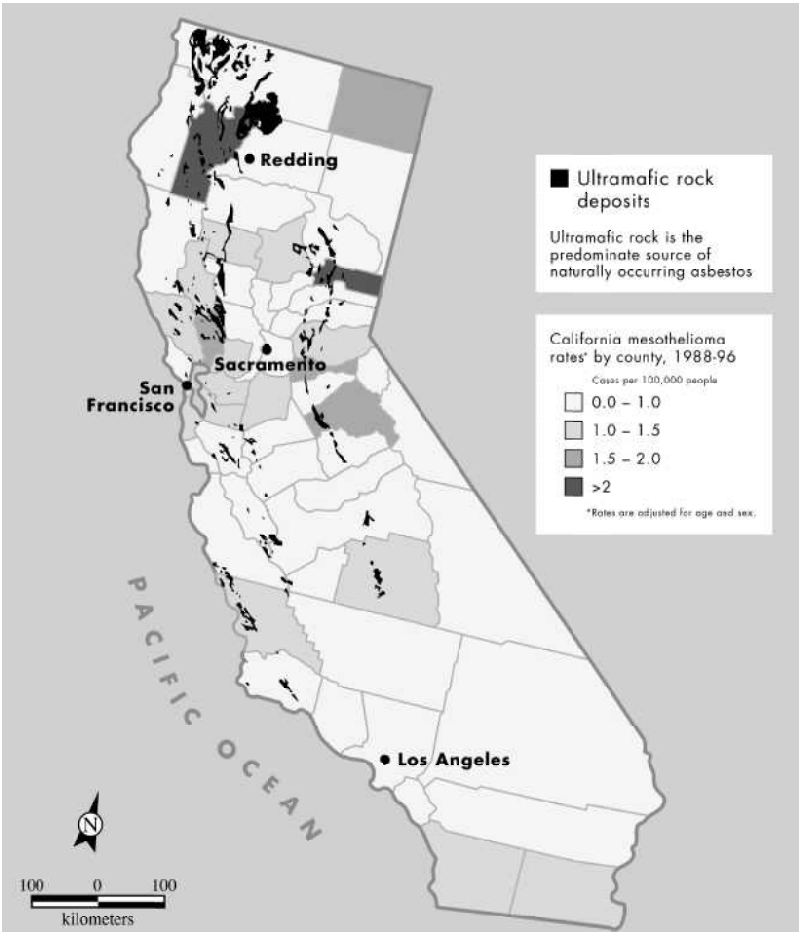

Figure 11. Combined epidemiological and geologic map showing spatial correlations between ultramafic rock and mesothelioma rates by county in California, developed by Pan et al. (2005), based on geologic information compiled by Churchill and Hill (2000). Reproduced from a graphic prepared by UC Davis (2006).

information that can be used to help interpret the potential contributions of NOA to disease using national-scale epidemiological data (Fig. 10), such as the state-scale study by Pan et al. (2005) (Fig. 11). The geologic occurrences of erionite—such as those noted by Sheppard (1996), in sedimentary rocks of the western United States—will also need to be factored in to epidemiological interpretations of asbestos-related disease.

The Dogan et al. (2006) study mentioned earlier provides another excellent example of how mineralogical characterization can facilitate the interpretation of epidemiological data. Similar studies that investigate the mineralogy, morphology, chemical composition, and accessory mineral content of asbestos as a function of the different geologic environments are also needed to help in the interpretation of regional- to national-scale asbestos epidemiological data sets. Epidemiological studies would also benefit greatly from detailed modern mineralogical and geochemical characterization of the materials in air samples collected from the breathing zones of potentially affected individuals.

Remote sensing techniques that enable mineralogical characterization can also provide useful information on the distribution of potential asbestos-forming minerals within regions geologically favorable for NOA. For example, Swayze et al. (2004) used AVIRIS, a hyperspectral remote sensing platform flown at 12,000 feet altitude, to successfully map rock outcroppings containing serpentinite and tremolite within mapped ultramafic rock units, and to map roads paved with quarried serpentinite well outside the mapped ultramafic rock units. Although this remote sensing technique can provide information of value to more local-scale epidemiological studies, it must be kept in mind that the technique so far cannot discriminate asbestiform versus non-asbestiform varieties of the same mineral, Further, it only maps minerals present at the immediate ground surface and requires extensive ground verification and field checking in collaboration with field geologists and mineralogists (Swayze et al. 2004).

Traditional mineralogical characterization methods have long been a crucial component of asbestos pathology studies, and have primarily been used to determine the mineralogical type and morphology of asbestos fibers found in tissue or BAL samples. There are interesting opportunities for the application of emerging mineralogical characterization technologies to asbestos pathology. For example, field emission scanning electron microscopy (FESEM) should permit higher resolution characterization of the surfaces of fibers obtained from tissue burden, and may provide further indications of the extent of chemical interactions between the fibers and physiological fluids (such as leaching or other chemical breakdown of the fibers). Detailed textural and compositional analysis of the interface between fibers and their coatings in asbestos bodies using FESEM may provide insights into the question whether fibers are active or passive participants in the formation of the asbestos bodies, by looking for evidence of leaching, replacement or other fiber-fluid reactions. High-resolution characterization of fibers in tissue sections using techniques such as X-ray absorption spectroscopy (Table 4) or Raman microspectroscopy (Centeno et al. 2005b) should be extremely helpful in understanding the distribution and (in the case of XAS) oxidation state of potentially ROS-generating species such as iron, chromium, and others in the fibers and adjacent tissues, thereby increasing the understanding of how fibers and their contained metals may contribute to chronic bioreactivity *in vivo*.

Earth science methods and techniques can contribute in several ways to enhanced interpretation of *in vivo* and *in vitro* toxicity tests and assays. Hochella (1993) cites 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. Nonetheless, it is rather apparent that many modern toxicological studies still do not recognize the potential for, account for, or rule out possible variability in test results introduced by geologic variability or differences in sample processing methodologies. As noted by Plumlee and Ziegler (2003, 2006) and Ziegler et al. (2002), potential geological variability within and between asbestos test materials includes differences in morphology, trace element content, oxidation state of redox-active species (i.e., Fe, Mn, Cr, As, W, others), accessory minerals, contaminants introduced by processing, and other characteristics. These differences can occur between samples of the same mineral from different samples in the same locality, between samples of the material from different localities of the same geologic environment, and between samples of the same mineral collected from different geologic environments of formation (i.e., as described by Van Gosen 2006b). Hence detailed mineralogical and chemical characterization of the source materials used for asbestos-related toxicity studies is crucial, as is factoring of important geological and mineralogical characteristics into the interpretation of the toxicological results. There is also a role for mineralogical, chemical, and redox characterization of fibers and asbestos bodies (as well as their elemental constituents) in tissue samples and cell cultures at the end of the toxicity testing. When compared to the original mineralogical and chemical characteristics of the source materials used in the testing, coupled with information determined in various physiological or

cellular assays, this information should provide valuable insights into fiber-fluid or fiber-tissue reactions and their potential links to toxicity.

UPTAKE OF HEAVY-METAL TOXICANTS FROM EARTH MATERIALS

A considerable amount of attention has been given in the health literature to the toxicity effects of lead, arsenic, mercury, chromium, cadmium, nickel, aluminum, and other metals (such as manganese, vanadium, tungsten, and others) in forms to which workers are commonly exposed in the workplace, or in highly soluble salt forms that are easily absorbed and that therefore can be readily assessed for toxicity effects. However, with the exception of lead, arsenic, and mercury, the uptake of heavy metals from earth materials and their resulting health effects have typically received less attention. We will use lead as an example of the ways that the earth and health science methods summarized in Table 4 have been or can applied to understand the uptake of heavy metals from earth and environmental materials.

Uptake of lead from earth and environmental materials

It has been readily demonstrated by a diverse array of studies over the years that lead, depending upon its form, can be readily taken up, absorbed, and cause toxicity via ingestion of lead-bearing soils, mine wastes, smelting byproducts, leaded gasoline combustion byproducts, and other earth or environmental materials. Likely mechanisms of exposure include involuntary ingestion of particles via hand to mouth contact, involuntary ingestion of deposited particles cleared from the respiratory tract by mucociliary action, ingestion of soil particles on poorly cleaned vegetables, and, more rarely, geophagia.

Biomonitoring. Biomonitoring studies have traditionally focused on measurements of blood lead levels (BLL), such as in individuals who demonstrate symptoms of lead toxicity or who have potentially been exposed to a known source of lead in the environment. If elevated BLL (at present, BLL > 10 μg/dL are considered elevated) are found, then investigations are typically undertaken to determine potential sources for the lead exposure; these source characterization studies routinely have involved measurements of bulk lead concentrations in the material(s) of interest, and have increasingly involved more detailed mineralogical characterization or chemical speciation studies to determine the form(s) of the lead. For example, Mielke (1999) and Mielke et al. (2004, 2006, and references therein) noted that 20-30% of the children living in inner-city New Orleans prior to Hurricane Katrina had elevated blood lead levels and that there was a direct correlation between child blood lead and residence in census tracts with elevated soil lead. They also noted a direct correlation between elevated soil lead and elevated lead in interior house dusts. The source of the lead in the soils and blood is likely lead in paint (dispersed into the soils as a result of paint removal practices from building exteriors), and possibly remnant leaded gasoline combustion products remaining in the soils.

There are a variety of shortcomings of BLL biomonitoring, such as the short half life (21-30 days) of lead in blood that precludes determination of non-recent exposures, and the remobilization of lead from the skeleton, which can obscure blood lead from recent exposures. These shortcomings are leading to the application of analytical methods from the earth sciences to examine records of past lead exposure recorded in the bones or teeth. For example, Arora et al. (2006) found that the spatial distribution of lead in teeth dentine reflected blood lead levels measured at birth and one year of age, using laser-ablation ICP-MS and confocal laser scanning microscopy; they concluded that the spatial distribution of lead in human primary teeth may be useful in obtaining temporal information on possible lead exposure during pre- and neonatal periods.

Tracking sources of blood lead using earth science methods. Radiogenic lead isotope analysis methods were developed originally for earth science applications, but have now

become a common tool in the biomonitoring toolkit. They are used quite widely and effectively to infer exposure sources for blood lead (Gulson et al. 1994, 1996a). They also can aid in the understanding of physiological processes by which lead is taken up, stored, and remobilized in the body (i.e., Gulson et al. 1996b).

In vivo lead uptake studies. Whereas biomonitoring can provide information on past or ongoing lead exposures, it is also highly desirable to be able to anticipate potential lead uptake that may result from future or present but unrecognized exposures to lead in a variety of specific source materials. Due to the complexity of chemical conditions in the human body, *in vivo* tests are viewed by toxicologists as perhaps the most useful means to assess and predict potential absorption of lead by children from various source materials. Casteel et al. (2006) provided a very recent summary of *in vivo* lead uptake tests in which juvenile swine were fed various lead-contaminated soils and soluble reference material (lead acetate) twice a day for 15 days. The resulting lead uptake, measured as relative bioavailability (RBA, compared to the amount of lead uptake from soluble lead acetate reference material) was assessed though measurements of blood lead during the study course and analysis of lead in liver, kidney, and bone samples collected at sacrifice following the administration period. The soil materials from various mining- and smelting-related superfund sites were well characterized to understand the mineral phase, particle size, and matrix association of the lead in each of the samples. The study found that the RBA of lead from the soils is a strong function of the lead mineralogy (Fig. 12): lead that is tied up in cerussite (lead carbonate) and with manganese oxides is highly bioaccessible, whereas lead in galena (lead sulfide), anglesite (lead sulfate) and mixed lead-metal oxides and silicates, and iron sulfates, is relatively non-bioaccessible. Casteel et al. (2006) concluded that their data were not sufficiently well defined that RBA could be predicted based solely on the lead mineralogy and speciation. As discussed by Plumlee and Ziegler (2003, 2006), there are other factors in addition to the mineralogic host, particle size, and associated matrix that may influence biosolubility and bioaccessibility of lead and other metals, such as the texture of the mineral host, and the presence of absence of other trace elements in the mineral.

In vitro bioaccessibility tests. Because *in vivo* studies are quite expensive, time-consuming, and logistically complicated, *in vitro* extraction tests using simulated body fluids (sometimes termed physiologically-based extraction tests, or PBET) have been used to model bioaccessibil-

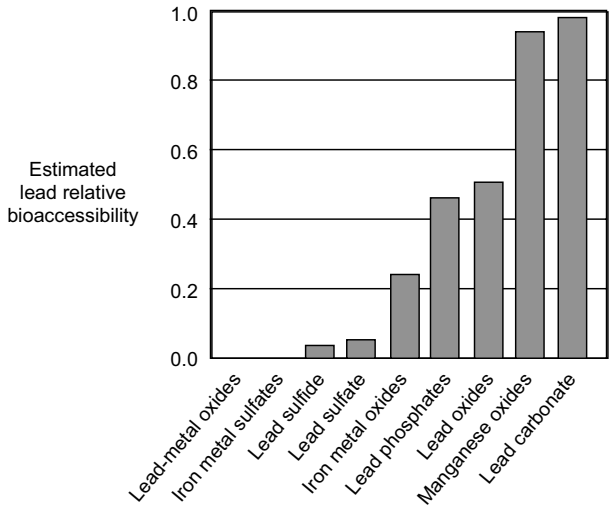

Figure 12. Plot from Casteel et al. (2006) showing the relatively bioavailability of lead from soils (determined by swine uptake studies) as a function of the lead-bearing minerals present in the soil.

ity of lead, other metals, and some organic toxicants in a variety of earth materials. Numerous studies have examined lead bioaccessibility from soils, mine wastes, and smelter byproducts by using a variety of different extraction methods, simulated gastrointestinal leachate fluid recipes, and solid:leachate ratios (i.e., Hamel et al. 1999; Ruby et al. 1999; Oomen et al. 2002, 2003, 2006; Shroder et al. 2004; Drexler and Brattin 2006; references in Plumlee and Ziegler 2003, 2006). Some of these tests model the entire passage through the gastrointestinal tract, by progressively subjecting a sample of the earth material of interest to simulated saliva for several minutes, followed by simulated gastric fluid for 1-2 hours, and then simulated intestinal (duodenal) fluids for 3-4 hours (i.e., Hamel et al 1999; Oomen et al. 2006). These tests can also be modified to simulate lead bioaccessibility and absorption in fasted versus fed conditions (with the addition of infant formula supplemented with sunflower oil), because metal bioaccessibility and absorption is generally greater in fasted than in fed conditions (Oomen et al. 2006).

Shroder et al. (2004) and Drexler and Brattin (2006) summarize a simpler test that was developed in conjunction with, and best models results of, the *in vivo* juvenile swine study discussed in the previous section (Casteel et al. 2006). This test uses a simple simulated gastric leach with hydrochloric acid and glycine; key features are that the pH must be maintained near 1.5, and that the test is most specific for lead.

Oomen et al. (2006) provide an excellent overview of the various tests, including a comparison of the saliva-gastric-intestinal tests versus gastric. For example, tests that only examine metal bioaccessibility in the gastric compartment overestimate total metal bioaccessibility, due to the diminished metal solubility and hence diminished bioaccessibility in the higher pH conditions of the intestinal tract. Also, soils with lead speciation and mineralogy not previously examined, as well as soils containing metals of interest other than lead, must ideally be calibrated against *in vivo* uptake tests to maximize the accuracy of the predicted bioaccessibility values. Although not specifically discussed by Oomen et al. (2006), it is possible that factors such as the amounts of iron-oxide particulates in the earth material may influence lead solubility and absorption in the intestinal tract by providing a substrate for lead sorption.

Lead uptake models have been developed to help estimate potential risk from exposure to lead-rich sources at specific sites. Examples include the US EPA Integrated Exposure Uptake Biokinetic Model for Lead in Children (IEUBK) (EPA TRW 1999, and references therein), and the International Commission on Radiological Protection (ICRP) Pb model (see example of its use and references in Abrahams et al. 2006). These models predict blood lead levels in children that would result from consumption of lead-containing particles from a variety of site-specific sources, including contaminated soils, lead paint chips, dust, foodstuffs, etc. Where data on these sources are not available, default values are assumed. The models also typically assume a default value for lead bioavailability (30% in the IEUBK model), which can be modified with the use of well-constrained bioaccessibility data developed through site-specific animal uptake or *in vitro* bioaccessibility testing (EPA TRW 1999).

Figure 13 compares the total lead content of and amounts of lead leached from a variety of earth materials by a simple gastric leach (our unpublished data, obtained primarily following the protocols of Shroder et al. 2004, and Drexler et al. 2006). Compared are: two samples of lead-zinc mine wastes from the Kabwe, Zambia lead-zinc mine (samples provided by Dr. Gary Krieger); NIST (National Institute of Standards and Technology) Butte, Montana soil standard, affected by copper- and arsenic-rich mine wastes; two urban atmospheric particulate standards collected by the in the mid-1970's in St. Louis, Missouri, and Washington, D.C.; a sample of the fine fraction of ballast lining a subway railbed; a NIST coal fly ash standard; two NIST soil standards with known contamination from lead paint chips; two edible soils purchased in a market in Kabwe (samples from Dr. Gary Krieger); a sample of ash left after a wildfire in ponderosa pine forest, Colorado front range (provided by Dr. Deborah Martin); and a sample of lake-bed dust from Owens Lake, California (provided by Dr. Marith Reheis). The

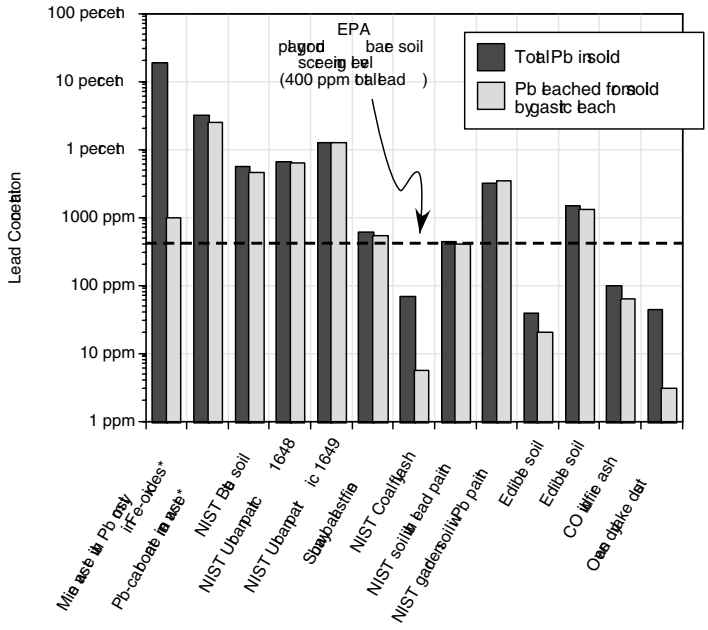

Figure 13. Our unpublished data on bulk metal concentrations and metal bioaccessibility from diverse earth materials indicate (in agreement with studies such as Casteel et al. 2006) that there can be substantial differences between the total lead concentration and lead bioaccessibility between different earth materials. Total metals were determined by ICP-MS following 4-acid digestion. Most of the leach measurements were made using the physiologically based gastric-fluid extraction test found to best reproduce lead uptake by swine (Casteel et al. 2006; Drexler and Brattin 2006); one part solid was added to 100 parts by weight simulated gastric fluid (HCl, glycine), and the mixture rotated at 37 °C for 2 h. Leach tests for samples indicated by the asterisk (*) were made using an NaCl-HCl simulated gastric fluid at 1 part solid to 40 parts gastric fluid. Lead concentrations in the leachates from both tests were recalculated to milligrams leached per kilogram solid for direct comparison to the total lead concentrations. In the NaCl leach tests, the pH shifted to substantially higher values (pH 4-5) due to the higher solid:liquid ratio and abundant carbonates in the samples; as a result, the amounts of lead leached should be an underestimate.

results show that Pb-Zn mine wastes (particularly those with high levels of lead carbonate), urban atmospheric particulates from the 1970's, and soils containing lead paint chips have both high to very high lead contents, as well as high lead bioaccessibility; many samples have lead contents far above the 400 ppm EPA soil screening level for bare playground soil. The urban particulate standards have elevated lead levels and very high lead bioaccessibility due to the presence of combustion byproducts of leaded gas, which was banned in the 1970's; hence most modern urban atmospheric particulates should have substantially lower lead levels than the NIST standards. The two mine waste samples illustrate the difference in lead bioaccessibility between lead largely tied up in iron oxides (less soluble in the gastric fluids) and lead tied up largely in lead carbonates (highly soluble in the gastric fluids). The African edible soil sample with elevated lead was purchased in a market near the now-closed lead-zinc mine from where the two Kabwe mine waste samples were obtained, and so it appears that the edible soil may have been produced from a soil contaminated by mine wastes or from a pre-mining soil developed on lead-mineralized rocks. The elevated lead levels and high bioaccessibility of the lead are obviously a source of health concern, as the soil is consumed mostly by pregnant women at a rate of tens to hundreds of grams per day; this could translate into the consumption of many tens to hundreds of milligrams of bioaccessible lead per day.

Lead uptake from earth materials via inhalation exposure? While many tests have been carried out to investigate the potential uptake of lead from earth materials by ingestion, far fewer have investigated potential lead uptake from earth materials via inhalation exposure (see summary in Plumlee and Ziegler 2003, 2006). We have investigated biosolubility of and metal bioaccessibility from a number of different earth materials using simulated lung and serum-based fluids, and have rather consistently found that lead does not show appreciable bioaccessibility in these simulated fluids (see the example of Owens Lake dusts shown in Fig. 14). In part, this may result from the lesser extent to which lead-bearing phases are solubilized in these pH 7.4 fluids (in spite of the abundance of myriad organic ligands available to complex the lead). However, it also likely results from the reaction of any solubilized lead with phosphate in the fluids to precipitate an insoluble lead phosphate phase. In contrast to lead, however, these tests suggest that oxyanion-forming (and potentially toxic) metalloids

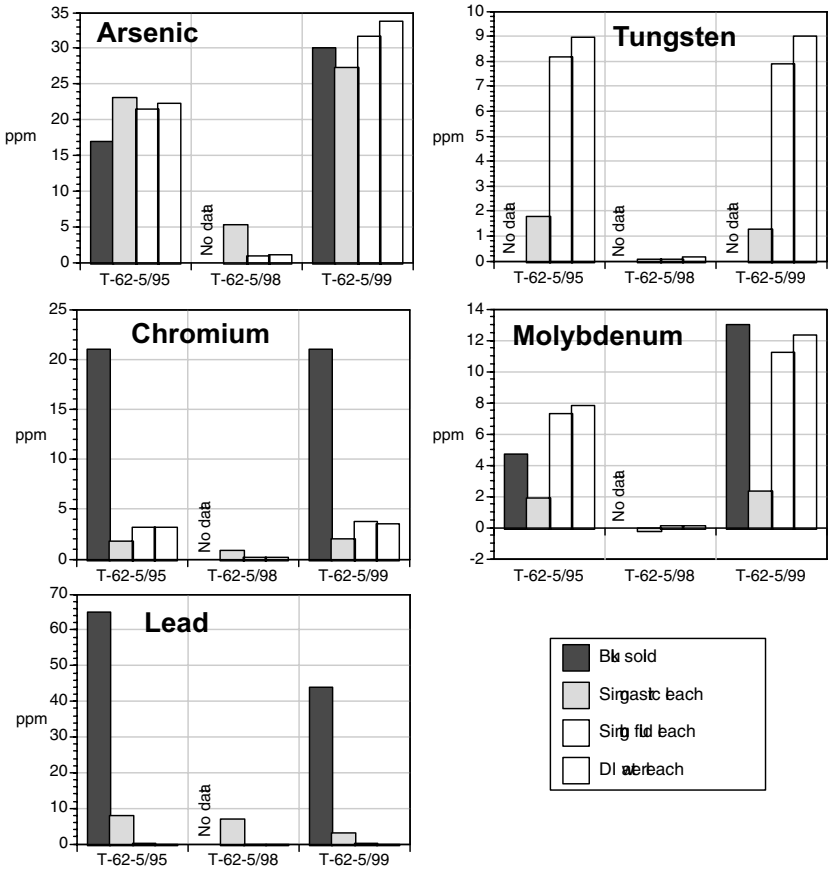

Figure 14. Our unpublished data comparing results of leach tests using simulated lung, gastric, and serum-based leach fluids of dust samples collected near Owens dry lake, CA, show that oxyanion species such as arsenic may be effectively leached by near-neutral pH fluids lining the lungs, due to their enhanced chemical mobility at near-neutral pH values. In contrast, lead is typically not leached by the simulated lung and serum-based fluids, due primarily to lead's limited solubility at pH 7.4 and its reaction with phosphate in the fluids to form insoluble lead-phospate precipitates. Lung and serum-based fluid compositions are listed in Plumlee and Ziegler (2003, 2006). All simulated lung fluid tests were run using a 1:40 solid:liquid ratio for 24 h at 37 °C, with continuous rotation of the sample container.

such as arsenic, chromium, molybdenum, tungsten and antimony (not shown) are relatively bioaccessible in the simulated lung and serum-based fluids (Fig. 14), due to the enhanced mobility of the oxyanion species at pH 7.4. We are currently evaluating metal bioaccessibility from earth materials in acidic simulated lysosomal fluids, as a simplified proxy for potential metal uptake via particle phaogcytosis.

SUMMARY

In this chapter, we have provided a comparatively brief overview of the myriad potential geochemical and biochemical processes that can occur when earth materials come into contact with body fluids via inhalation, ingestion, or percutaneous exposure routes. We have also shown how a wide variety of earth science methods have been and can be integrated with health science methods to better understand the potential health effects that might be associated with exposure to diverse earth materials.

As noted by Plumlee and Ziegler (2003, 2006), it is possible to group individual earth material components according to how they behave *in vivo*, as well as by similarities in how they trigger toxicity:

- Bioreactive earth materials can substantially modify the chemical composition of body fluids and tissues, to produce tissue irritation or more serious alkali or acid burns.
- Solubilization of bioaccessible toxicants from earth materials and their subsequent absorption can produce toxic effects in the body.
- Exposure to earth materials that are insoluble (biodurable) in body fluids can trigger toxic responses as the body attempts to clear the materials.
- Pathogens associated with earth materials can trigger disease.
- The body's immune response to the earth materials or toxicants contained within the earth materials can trigger a toxic response.

All of these different these types of health effects are strongly influenced by the forms in which earth materials are delivered to the body (mineralogy; particle size and morphology; particle solubility, alkalinity, acidity; oxidation state of contained constituents; and others). These health effects all also ultimately require some level of chemical interactions between the earth materials and body fluids.

However, most earth materials are complex mixtures of many different components, each having a particular mix of bioreactivity, biosolubility, and biodurability characteristics. Potentially complex chemical interactions between the various earth material components and the body's fluids may result. Hence, as the potential health effects of complex earth materials are assessed, it should always be kept in mind that the integrated physical and chemical characteristics, chemical behavior *in vivo*, and resulting toxicity effects of the whole material may be substantially different from those of its individual components..

These conclusions implicitly require important roles for the earth scientist in helping to both characterize earth materials and understand geochemical processes in the context of the physiological processes of the human body. Many studies have been carried out to address this complex but fascinating topic; however, as indicated by the sections on asbestos and lead, there are many unresolved questions remaining. There should therefore be ample opportunities for fruitful future collaborations to occur between geochemists, toxicologists, physiologists, epidemiologists, and other biomedical disciplines.

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