Mineral Properties and Their Contributions to Particle Toxicity

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It has been recognized since at least as early as the mid-1500s that inhaled minerals (i.e., inorganic particles) can pose a risk. Extensive research has focused on the biological mechanisms responsible for asbestos- and silica-induced diseases, but much less attention has been paid to the mineralogical properties and geochemical mechanisms that might influence a mineral's biological activity. Several important mineralogical characteristics control a mineral's reactivity in geochemical reactions and are likely to determine its biological reactivity. In addition to the traditionally considered variables of particle size and shape, mineralogical characteristics such as dissolution behavior, ion exchange, sorptive properties, and the nature of the mineral surface (e.g., surface reactivity) play important roles in determining the toxicity and carcinogenicity of a particle. Ultimately, a mineral's species (which provides direct information on a mineral's structure and composition) is probably one of the most significant yet most neglected factors that must be considered in studies of toxicity and carcinogenicity. — Environ Health Perspect 105(Suppl 5): 1003–1011 (1997)

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Introduction

In his 1556 treatise De Re Metallica, Georgius Agricola noted that miners exposed to dust from some mines had increased risks for various diseases, including consumption (1). Although it is not clear from Agricola's description whether or not consumption refers specifically to tuberculosis or more generally to pneumoconiosis, it is interesting to note that the links both between dust exposure and tuberculosis and between dust exposure and pneumoconiosis were borne out in later studies, including work 400 years later by King and co-workers (2–8). By the time of King and co-workers, it was generally recognized that inhaled minerals can initiate a number of responses, including the formation of ferruginous bodies (9–12), fibrosis (3, 4, 6–8, 13–17), and more recently, carcinogenesis (18–21).

Even (perhaps especially) at these early stages of research on mineral-induced pathogenesis, it was recognized that the key to understanding why some minerals are toxic or carcinogenic is to link mineralogical properties with biological processes. Much of this insight came from the work by King and co-workers, through their collaborations with G. Nagelschmidt, a mineralogist, and to a lesser extent V.M. Goldschmidt, who is considered by many to be the founder of modern geochemistry. Through these collaborations, King and co-workers investigated the biological activity of a list of minerals that is truly impressive: olivine (22), kaolinite minerals (4, 6, 14), micas (2), various silica polymorphs (including quartz, tridymite, cristobalite, and amorphous silica) (5, 7, 23–25), various forms of aluminum and iron oxides and hydroxides (including boehmite or γ-AlOOH, corundum, or α-FeOOH—which is isomorphous with hematite, γ-Fe2O3, goethite, or α-FeOOH, and lepidocrocite or γ-FeOOH) (3, 8), and berellite or AlPO4 (8).

As demonstrated by their use of mineral species names to describe their materials, King and co-workers must have recognized that the structure and composition of a material (the two characteristics that define a mineral species) are critical to determining the way in which a material interacts with its environment. This is a fundamental principle in the geosciences, where it has long been recognized that each mineral species possesses unique properties (derived from its crystal structure and/or composition) and that these properties determine how a mineral interacts with its environment.

In this paper, I address a number of mineralogical properties that affect how a mineral interacts with its environment. Some of these properties have been shown to affect toxicity and carcinogenicity, and some are known to be important in geological processes but have not been explored with respect to biological processes. An underlying principle throughout this paper is that pathogenesis originates at the mineral–fluid–cell interface, so interactions between a mineral and fluid or a mineral and a cell may eventually lead to disease. These interactions range from indirect interactions between a mineral surface and extracellular or intracellular fluids (including fluids associated with phagosomes and/or lysosomes) to direct interactions between a mineral surface and cell–surface receptors or other components of a cell's membrane. To gain insight into what mineralogical properties are important for a mineral's role, we can borrow from the geosciences where a large range of mineral–fluid interactions have been and continue to be studied. I discuss briefly several properties that are commonly addressed—particle size/shape, mineral species (structure/composition), dissolution, and surfaces. I also discuss two properties that are seldom addressed—cation exchange and oxidation/reduction. All these properties are known to affect the way in which a mineral interacts with a geological fluid and are likely to play roles in mineral–fluid interactions in the lung.

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*Mineral species are applied in much the same way as animal/plant species: A mineral species is the most specific distinct division within the classification scheme for minerals. It defines a specific crystal structure and a composition or compositional range. Sometimes subspecies (termed varieties) are defined based on characteristics such as morphology or crystal habit (e.g., crocidolite is the varietal term for asbestiform blue asbestos).
Mineralogical Properties Important in Toxicity

Solids can be divided into two broad categories based on the property of translational periodicity: crystalline and noncrystalline (or amorphous). Translational periodicity is the characteristic that allows the extended structure existing throughout a single-phase particle to be represented by a smaller subunit that is translated along non-coplanar vectors in three dimensions, in the same way that a wall might be represented by a brick or cinderblock that is translated in two dimensions. Translational periodicity is necessary for a structure to diffract X-rays constructively (which is why proteins must be crystallized for structural analysis), but it also imparts a wide range of properties to minerals that differentiate them from amorphous materials. In fact, crystallinity appears to be an important factor in toxicity/carcinogenicity, as exemplified by the higher biological reactivity of some types of crystalline silica compared with noncrystalline silica (26).

Much of our insight into how a mineral interacts with a fluid comes from observations on geological systems. Reactions involving minerals in geological environments are often mediated by fluids; consequently, mineral–fluid interactions are among the most widely studied phenomena in mineralogy, geochemistry, and other branches of the geosciences. Our current understanding of these phenomena has led to several important geological tenets that are equally important in mineral toxicity/carcinogenicity:

- a mineral affects its environment;
- a mineral is affected by its environment;
- mineral species is a critical descriptor of a material’s overall characteristics;
- the properties of a mineral species can vary between samples.

Although these tenets may appear self-evident (as they undoubtedly did to King, Nagelschmidt, Goldschmidt, and their co-workers), they serve as important reminders that mineralogy is an integral component of mineral toxicity. As such, care must be taken to ensure that mineralogical issues in a study are as adequately addressed as biological issues. However, it also means that the mineralogical approaches to toxicity studies can provide important new insights into the molecular processes that occur. For example, the first tenet embodies the notion that a mineral can induce reactions in a cell or physiological fluid. Hence, by appropriate manipulations of mineralogical variables, one can alter a biological response in a systematic way to reveal the mineralogical and biological molecular mechanisms (in much the same way that one manipulates the biological variables to reveal mechanisms). The second tenet embodies the notion that the type of a mineral is changed by a reaction preserves information about the reaction. Hence, one can learn something about a mineral–fluid–cell interaction by observing not only how the cell and fluid respond but also by observing how the mineral responds.

These principles form the motivation for the remainder of this paper, which will attempt both to address some of the mineralogical properties important in toxicity and to illustrate how a combined mineralogical and biological approach can improve our understanding of these complex processes. The first three topics (mineral species, particle size and shape, and sample history) cover properties that in general should be determined for every sample studied. The remaining four topics (ion exchange, oxidation/reduction, dissolution, and surfaces) are additional mineralogical factors that are key components of a mechanistic model for mineral-induced pathogenesis. I focus primarily on the first two topics because the last two topics are covered extensively elsewhere (including other articles in this volume that address particle surfaces).

Mineral Species: Structure and Composition

A determination of the mineral species used in a specific study is the bare minimum required in terms of sample characterization. Although mineral species often takes a back seat to particle size and shape (discussed below) in most studies on toxicity and carcinogenicity, it is, in fact, one of the most critical characteristics because it provides information on the bulk structure and composition of a material—the two most basic characteristics of a material that ultimately have a profound effect on many of the other mineralogical properties important in pathogenesis.

Both the structure and composition are needed to define a mineral species because neither alone is sufficient to describe the properties of a material; this is well illustrated by the minerals quartz, stishovite, and rutile. Figure 1 shows polyhedral representations for the structures of these minerals. Quartz and stishovite are compositionally identical (SiO$_2$) but have markedly different structures (Figure 1A–D). This structural difference imparts different solubilities (important in biodurability and possibly toxicity), different functional groups on the surface (related to different bonding strengths for various surface oxygen sites, which translates, for example, into different dissociation constants for protons on the surface), and different tolerances for various trace elemental contaminants (to name a few differences important in toxicity). Stishovite and rutile are structurally identical (Figure 1B,D) but have different compositions (SiO$_2$ and TiO$_2$, respectively). This compositional difference affects solubilities, surface functional groups, and bulk oxidation–reduction characteristics, to a name a few. (Interestingly, stishovite and rutile are both nonfibrogenic and noncancerogenic, suggesting that this structure type may not elicit a pathogenic response. Although this observation has been alluded to often, no one has tested this mechanistic hypothesis by investigating systematically the many other materials with this structure such as pyrosilicate or MnO$_2$, cassiterite or SnO$_2$, argyrite or GeO$_2$, and marcasite or FeS$_2$.)

The asbestos literature has evolved to the point where the use of terms like crocidolite (the asbestiform variety of the mineral species riebeckite), amosite (a commercial term mostly referring to the asbestiform variety of the mineral series cummingtonite–groeninite), asbestiform tremolite, and chrysotile is commonplace. Similarly, studies on the oxides of silicon (typically SiO$_2$ or silica) often use proper mineral species terms, like quartz, tridymite, and cristobalite. Nevertheless, since the days of King and co-workers (who were faithful to the use of mineral species names for silica polymorphs as well as for other minerals in their studies), the use of terminology has become much less rigorous. Now the use of the nondescript term silica is not uncommon and the use of chemical terms (and not mineralogical terms) for other materials is the norm—e.g., studies on the oxides of titanium almost always use
the term titanium dioxide to describe a material. This lax approach to sample description can lead to a false sense of confidence in the ability to interpret results from various studies. For example, one is led to believe that the results for titanium dioxide in one study can be compared with results for titanium dioxide in another study. In fact, TiO₂ or titania crystallizes in at least seven different polymorphs (i.e., different structures), including rutile (Figure 1C,D), anatase, brookite, and TiO₂ (B) (31) for figures of these last three polymorphs. In addition, titanium oxides with stoichiometries different from TiO₂ occur (i.e., where the oxidation state of Ti is not uniformly Ti⁴⁺). Each of these forms of titanium oxide has different properties (31). For example, anatase is used as a catalyst (32,33) and photocatalytic (34–36). Differences in biological activities have also been noted for the polymorphs of TiO₂ (37–39). Nevertheless, it is commonplace to read that a particular study used TiO₂ as a negative control. Clearly, in the absence of information on the crystal structure of a material, the use of a chemical term such as titania or titanium dioxide is inadequate information to provide for a sample used in a toxicity study.

Although mineral species is one of the most critical characteristics to be determined for a sample used in a toxicity study, there are cases for which the use of a mineral species name (which defines the ideal composition and bulk structure) is insufficient information for describing a sample. With respect to composition, this can occur when the mineral species is defined for a range in composition or when the composition of the sample deviates from the ideal stoichiometry. The first case is well illustrated by the asbestiform amphiboles. For example, asbestiform riebeckite (or crocidolite) has an ideal end-member composition of Na₂Fe³⁺Fe²⁺Si₄O₂₂(OH)₂, but the mineral species riebeckite is actually defined over a much broader range of composition, which allows for a) potassium and sodium to partially occupy the "A" site, which is omitted in the ideal formula; b) up to 50% replacement of the iron by magnesium; and c) limited other substitutions for sodium, iron, silicon, and hydroxyl (40). These compositional variations can have profound affects on the sample’s properties, including toxicity. For example, one can easily imagine that a significant replacement of iron by magnesium would have an impact on the particle’s ability to drive the Fenton-type reactions that are currently believed to explain crocidolite’s extreme biological activity (41,42). Hence, a compositional analysis must be provided for the particular crocidolite sample used in a toxicity study. The second case can occur even for well behaved minerals like quartz, which can have up to a few wt-% of elements like Al and Fe (28). These minor and trace elements can have a significant impact on the biological reactivity of quartz (43).

In some cases, mineral species inadequately describes a material’s structure because the presence of defects (which are deviations from the ideal structure) introduce significant variation into the material’s properties. For example, ostensibly non asbestiform riebeckite and asbestiform riebeckite (crocidolite) share the same structure. However, samples of crocidolite generally have a large proportion of chain-width defects, which imparts unique mechanical properties on crocidolite (i.e., crocidolite is flexible whereas nonasbestiform riebeckite is not) (27). These defects can additionally impart other differences in the properties between the two materials (e.g., the diffusion of cations within and the dissolution properties of amphibole are affected by chain-width defects, both of which will affect the release of iron to the fluid). Hence, the differences in biological activities noted for these materials (44,45) cannot be uniquely attributed to particle morphology, as is often done.

**Particle Size and Shape**

Particle size and shape are universally considered important factors in pathogenesis and are faithfully reported in most studies. There are several understood (or partially understood) mechanisms by which size and shape may influence toxicity and carcinogenicity, including fate of the particle (from deposition to physical translocation to cell-mediated translocation), surface area, types of reactive sites, particle–cell interactions, and catalysis.

Particle size and shape exert a major control on deposition, translocation, and clearance (i.e., the fate of a particle following inhalation). Deposition is affected by a
combination of physical limitations imposed by the constricting airways—which reduce to approximately 50 μm by the time they reach the alveolar ducts (46)—and aerodynamic and gravitational factors—which control processes such as impaction, settling, interception, and diffusion (47). These processes lead to heterogeneous particle-size deposition throughout the conducting airways and lungs. For example, larger particles (>0.2 μm) are dominantly deposited in the nasopharyngeal region (47), whereas smaller particles are deposited in the respiratory tract. This translates into approximately 10 μm as an effective maximum size for respirable particles in humans and approximately 5 μm as an effective maximum size for respirable particles in rats (48). Translocation (particularly from the airways through the parenchyma to the pleura) is also affected by particle size and shape as demonstrated by the observation that fibrous particles are commonly found in the pleural space. Finally, clearance mechanisms—e.g., dissolution rate, which is an important clearance mechanism for rapidly dissolving materials like chrysotile (49), and cellular clearance mechanisms such as phagocytosis and translocation—are strongly limited by particle size and shape.

Size and shape also determine the surface area of a particle and, perhaps more importantly, the surface area per unit volume or per unit mass of the sample. Particle volume (and hence mass) scales with the cube of a particle size, whereas the surface area of a smooth particle scales with the square of particle size. In other words, small particles have larger surface areas per unit mass than larger particles, which means that smaller particles have more reactive surface available on a per-mass basis. Consequently, a number of researchers have argued in favor of comparing toxicity of materials on a per-fiber (or per-particle) basis rather than on a per-mass basis (50). "Per surface area" is probably a more defensible basis on which to compare results, but only a few studies have endorsed this approach (51).

Another important aspect of particle morphology relates to the nature of reactive sites on the particle surface (as discussed below), because a particle's morphology determines the exposure of various reactive sites. For example, the active sites associated with the ends of crocidolite fibers (which differ dramatically from the active sites associated with the sides of the fibers) have lower exposed areas than they would in a case where the crocidolite formed sheet-like particles normal to the fibers (Figure 2).

Recent work presented at this conference suggests that fiber length may affect particle-cell interactions by causing mechanical stresses on the cell surface (52). Mijailovich and co-workers hypothesize that the contact of a long fiber with alveolar epithelium that is in cyclic motion because of tidal breathing causes stresses on the cell that trigger a response.

Finally, a number of materials become effective catalysts when their particle size becomes extremely small (i.e., <1 μm). One component of this increased catalytic activity may relate to increased surface area; however, other surface-related properties of finely crystalline materials also vary dramatically from those of more coarsely crystalline materials. Similarly, biological activity apparently is altered by extremely small particle sizes. For example, Driscoll and Maurer (39) found that very fine-grained (<0.01 μm) TiO2 is more active than larger-grained (1 μm) samples of the same material.

**Sample History**

The surface of a particle can be significantly altered by processes related to the sample's history. For example, grinding of a material can produce freshly fractured surfaces with numerous high energy sites (e.g., unstrained bonds and steps/ledges), and these surfaces are known to be more reactive in geological environments (53). Similarly, these surfaces are more reactive in biological environments, and several studies have noted a distinct difference between freshly fractured materials and aged materials (54).

In addition to surface aging in air, however, there are a number of sample preparation techniques that have the potential to affect a particle's surface properties significantly, including sterilization processes (e.g., alcohol treatment, autoclaving, and dry heating) and suspension of samples in buffers or media. No studies have investigated systematically how these treatment methods affect various reactive sites. Nevertheless, it is important to document a sample's history thoroughly so that the potential impacts of various aspects of its history can be evaluated.

**Sorption and Cation Exchange**

One of the principle ways in which a mineral can interact with a fluid (particularly in the short term) is through an exchange of an element or molecule (e.g., by ion exchange). Ion exchange occurs when a sorbed species on the mineral exchanges with a similarly charged species in the fluid (55). This definition implies that any mineral has the potential to exchange ions with a fluid. Most minerals have only a limited capacity for cation exchange because sorption occurs only at the surface (i.e., adsorption). For such materials, the capacity for cation exchange is related to surface area, and the complexation of ions or molecules with the surface can have an important effect on a mineral's reactivity. Some minerals (e.g., zeolites), however, have much greater capacities for cation exchange for given masses because the ions can diffuse rapidly from the surface of the mineral to its interior, thereby enabling the entire particle to provide a buffering capacity.

As noted by various investigators (56,57), the extreme biological activity of erionite (45,58–60) and the interest in other zeolites (44,61–70) raises the question, "Does cation exchange play a role in mineral-induced pathogenesis?" Because cation exchange is one of the defining characteristics of zeolites (others being molecular-sieving capabilities, high catalytic potential, and high surface internal area accessible to small molecules). Cation exchange could play an important role in cellular responses through a number of mechanisms, including the buffering of cation (e.g., calcium) activity at the surface of a cell. Nevertheless, relatively little attention has been given to the potential role of cation exchange. Guthrie and co-workers (71) reported no noticeable difference...
in the colony-forming efficiency of rat lung epithelial cells exposed to a suite of cation-exchanged erionites (Na, K, Ca, and Fe³⁺) all derived from the same parent material. However, using the same suite of erionite samples, we have found that cation exchange may have an effect on cytotoxicity, gene response (as measured by steady-state levels of mRNA for c-jun), and apoptosis in some rat pleural mesothelial cells (Guthrie G, Timblin C, Mossman BT, unpublished data). For example, preliminary results suggest that Na- and K-exchanged erionite may be more cytotoxic at 72 hr than Ca- and Fe-exchanged erionite (Figure 3). Initially, one might conclude that cation exchange, which happens rapidly in simple aqueous solutions, would only be significant immediately after exposure. However, the kinetics of cation exchange in a complex biological fluid which contains molecules that could inhibit exchange by interfering with ion channels on the mineral surface are not known.

**Catalysis**

Minerals—particularly but not exclusively zeolites and some clays—are exploited extensively as catalysts. The mechanisms by which minerals function as catalysts generally relate to their ability to donate or accept electrons or protons, to provide a stabilizing surface (a template) for reacting components, and to exclude molecules of a specific shape or size from the catalytic sites. In other words, minerals can function in a manner similar to that of traditional enzymes.

The proton and electron donor/acceptor sites (the acid/base sites) of the mineral are commonly exploited and are responsible for the widespread use of zeolites as catalysts in the cracking of hydrocarbons. The acid/base characteristics of framework silicates such as zeolites are strongly influenced by the substitution of aluminum for silicon in the tetrahedral framework. This substitution can be charge compensated for in a number of ways, including the association of a proton with the underbonded oxygens around the aluminum. Hence, these sites (like many other surface sites on minerals) function in a manner similar to that of enzymes in that they can alter the apparent local activity (or thermodynamic concentration) of a species like hydrogen at a specific reactive site. A number of different such sites can exist on the surface of zeolite, and range from silanol groups (Si-O-H) to the aluminum equivalent (Al-O-H) to protons generally associated with an aluminum-exchanged tetrahedral site, e.g.,

\[
\text{H} + \text{Al-O-Si}
\]

The protons associated with each of these sites have different pK values. There recently has been much success in applying *ab initio* calculation methods to calculate the reactivity associated with such surface sites (72).

It has long been argued that hydroxylated surface sites (e.g., silanol groups) are responsible for the toxicities of the silica polymorphs because they function as hydrogen donors. In support of this is the fact that the hemolytic reactivity of quartz can be diminished (73) by treatment with polyvinyl-pyridine-N-oxide (PVPNO), a polymer that binds to proton donor sites.

**Oxidation-Reduction**

The transfer of electrons between a mineral and fluid drives a number of geochemical processes. In general, silicates and many other minerals are considered to be insulators (i.e., they do not conduct electrons rapidly). At higher temperatures (hundreds of degrees Celsius), some silicates begin to conduct electrons sufficiently rapidly to allow their electrical properties to be studied somewhat routinely. The oxidation/reduction properties of the amphibole asbestos minerals crocidolite and amosite have been studied extensively at high temperatures, beginning with the pioneering studies of Addison and co-workers (74–76).

Although they focused on higher temperatures (450–615°C), they studied the kinetics of the reaction down to 350°C and noted that oxidation can occur even at 0°C. At lower, physiological temperatures, the rates may be too slow to measure effectively in a laboratory experiment, but they may be sufficiently high to provide a chronic source (or sink) of electrons for reduction (or oxidation) of fluid species (e.g., to form free radicals).

Interestingly—and predictably based on mineralogy—the resistance of amphiboles varies strongly with crystallographic direction. Electron conduction occurs most rapidly along the length of the fibers (i.e., along the octahedral strips that contain iron). Crystallographically similar electron conduction pathways occur within the octahedral sheets of phyllosilicates like biotite (i.e., at the edges of the sheets readily formed by the dominant cleavage direction in micas), which is why micas are effective insulators normal to their sheets (they are exploited this way in capacitors) but have much lower resistance along their sheets.

Although most investigations of oxidation-reduction and conduction in silicates have focused on high temperatures, these processes are known to be important for a number of reactions at lower temperatures (e.g., < 50°C). For example, electron transfer reactions have been shown to be important in the weathering at ambient temperatures of minerals such as amphibole (77) and magnetite (78), in the formation of copper ore deposits (79), and in the sorption of metals such as Cr to the mineral surface at 25°C (80). Clearly, the transfer of electrons between minerals and fluids is important at physiological temperatures and, as shown in Figure 4, this redox process is strongly controlled by the crystal structure.

The propensity for a redox reaction to occur can be assessed by comparing the $E_H$
or redox values for the individual half reactions, which ultimately relate to the electrochemical potentials (E°) for the half reactions. Electrochemical potentials for aqueous reactions can be readily determined and have been tabulated for a number of half reactions. For example, [Fe^3+][aq] + e^- → [Fe^2+][aq] has an E° of 0.77 V (81). Unfortunately, the electrochemical potential for various redox reactions in minerals is poorly known. White and Yee (77) bracketed the electrochemical potential for Fe^3+→Fe^2+ in a hornblende amphibole at between 0.33 and 0.52 V under their experimental conditions. White and co-workers (78) determined the electrochemical potential for Fe^3+→Fe^2+ in a magnetite sample (-0.27 V at pH 7) directly by measuring the self-induced potential of a magnetite electrode (a procedure that requires a large single crystal). Ilton [(79,82); personal communication] found that the electrochemical potential for Fe^3+→Fe^2+ in biotite is probably close to the values determined by White and Yee for hornblende, based on the observation that Ag⁺ reduces vigorously (E° = 0.80 V; even at a concentration of 10 ppm), whereas Cu^2+ (E° = 0.34 V) reduces but much less vigorously.

The mechanisms by which a mineral can transfer electrons from within the crystal to the surface also must be known to evaluate mineral-catalyzed redox reactions in a fluid. An important component of the mineral-catalyzed redox is that the crystal must remain charge balanced (or at least close to neutral charge). Hence, for the oxidation of crystal-bound iron to reduce a solution-bound species, the reaction can be broken down into several steps:

$$\text{(Fe}^{3+}\text{)crystal} \rightarrow (\text{Fe}^{2+}\text{)crystal} + (\text{e}^-)\text{surface} \quad \text{(1)}$$

$$\text{(OH}^-\text{)crystal} \rightarrow (\text{O}^{2-}\text{)crystal} + (\text{H}^+)\text{surface} \quad \text{(2a)}$$

$$\text{(R}^+\text{)crystal} \rightarrow (\text{R}^-)\text{surface} \quad \text{(2b)}$$

$$\text{(O}^{2-}\text{)surface} + \square \text{crystal} \rightarrow (\text{O}^{2-}\text{)crystal} \quad \text{(2c)}$$

where □ designates a vacancy or unoccupied crystallographic site and R⁺ designates a cation site. The reactions are written with respect to changes within the mineral and where the surface represents the interface between the mineral and the fluid (e.g., an electron at the surface can transfer to the fluid). The electron-exchange reaction (Equation 1) is written involving iron, because this is the most common polyvalent cation in minerals. Equation 2 summarizes three possible mechanisms for maintaining charge balance within the crystal (74). Equations 2a and 2b maintain charge balance by diffusing a charged species out of the crystal. Hydrogen, because of its small size, would be the easiest of the possible cations to diffuse out of minerals such as amphiboles and, in fact, Addison and co-workers (74) proposed this mechanism for crocidolite oxidized at 450 to 615°C. Scott and Amonette (83) endorsed a slightly different mechanism in weathering conditions (i.e., low temperatures) whereby charge balance is maintained by dissolution of iron after oxidation (Equation 2b). In some materials (e.g., magnetite or Fe₃O₄) diffusion of hydrogen is not an option, so mineralogical changes occur. For magnetite, oxidation occurs through the formation of maghemite (78). The mechanism by which a mineral oxidizes has a profound effect on the rate of oxidation (i.e., on the rate of sustained electron transfer).

How, then, might electron transfer processes play a role in pathogenesis? Electron transfer involving the surface of minerals has been attributed to the increased biological activity and heightened formation of free radicals associated with freshly fractured quartz compared to aged quartz (54,84,85). Such a process produces a transient or acute burst in free radicals that ceases once the particle surface has been passivated (i.e., once the surface radicals have equilibrated). Electron transfer involving the internal regions of the crystal (through transfer between the surface and interior) has the potential to produce a sustained or chronic redox condition to drive formation of radicals in the fluid. In addition, once electron transfer to the fluid has occurred, iron release to the fluid (to maintain charge balance) could provide another mechanism for driving Fenton-type reactions. Several lines of evidence support the notion that electron transfer processes are important in pathogenesis. Fubini and co-workers (86) reported that magnetite will breakdown hydrogen peroxide, whereas hematite (Fe₂O₃) will not, which suggests that Equation 1 plays an important role in the formation of free radicals. Figure 4 shows a mica crystal that has reduced silver from solution to cause its precipitation at the redox-active edges. Similarly, in his descriptions of ferruginous bodies, Roggli (87) shows several particles of mica recovered from human lung (his Figures 3–18); the particles have become coated with a ferruginous material only at the redox-active edges of the crystals. Although the mechanism of ferruginous body formation is still not understood in its entirety, it is believed to relate to the breakdown of an iron protein such as ferritin (which can be denatured by a redox mechanism). It is interesting to note that asbestos bodies typically have more precipitate at their
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ends, which are crystallographically similar to the edges of mica and which are known to be the redox-active areas at higher temperatures.

Dissolution Behavior

Dissolution can be a significant component of particle clearance mechanisms and can cause the release to the lung fluid of ions such as iron, other metals, or other toxic elements. Dissolution is often used as a basis for differentiating nonhazardous from potentially hazardous minerals, where nonhazardous minerals have a low biodurability and, hence, do not remain in the lung for long periods of time.

Unfortunately, there are few data on the kinetics of mineral dissolution in biological fluids that are also based on mechanistic dissolution models for minerals. One such study was recently conducted by Hume and Rimstidt (49), who based their model on the release of silica as the rate-limiting step for chrysotile dissolution. Their dissolution rate model predicts that chrysotile fibers will dissolve completely in days to months under lunglike conditions.

It has long been recognized that mineral burdens in human lungs are not exactly representative of the dusts to which an individual is exposed [reviewed by Churg (88)]. For example, chrysotile miners typically have a nearly steady-state level of chrysotile in their lungs but a continuously increasing level of tremolite (a minor contaminant of the chrysotile ore). These observations are consistent with the rate model of Hume and Rimstidt, in that the steady-state levels observed represent competition between deposition and dissolution. Dissolution of minerals under these conditions is discussed in detail by Hochella (89).

Surfaces

Ultimately, the surface is that part of a mineral that interacts with a fluid or cell. For some materials, the structure at the surface can differ substantially from the structure exhibited by the bulk (89). These differences between the surface and the bulk can range from simple distortional relaxation of surface atoms to a completely different material on the surface. Frequently, a dissolving mineral will form a precipitate at the surface with a composition/structure that differs from the bulk material. Even chemically simple minerals such as quartz can have surfaces that are structurally different from the bulk (90, 91); at another extreme would be a fiber of amphibole asbestos, which likely has much of its surface covered by a phyllosilicate-like material that is both compositionally and structurally distinct from the bulk amphibole (27). Clearly, there is a large range of surface-related factors that can change the active sites on the surface, can affect binding/sorption processes on the surface, can affect dissolution characteristics, and can generally have an impact on a mineral's pathogenic potential. A detailed discussion of surface characteristics important in pathogenesis is beyond the scope of this paper, but some of these aspects are addressed in Guthrie (26, 28) and Hochella (89).

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