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Mineralogical characteristics of silica polymorphs in relation to their biological activities

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Numerous aspects of silica polymorphs can affect their biological activities, including periodic structures, compositional variations, dissolution characteristics, surface properties, and particle size and shape. For an understanding of mineral-induced pathogenesis from a mechanistic perspective, the links between these properties and biochemical processes must be elucidated. This paper presents some strategies for designing assays to evaluate these properties.

Key terms cristobalite, coesite, keatite, quartz, toxicity, tridymite, stishovite.

Each day, we are exposed to respirable mineral particulates derived from soil and rock. Numerous minerals, including several varieties of silica, have been studied with respect to pulmonary disease, and many appear to be toxic. Biological activities of minerals vary extensively, irrespective of particle morphology (1). This variation in biological activity reflects factors, such as structure, composition, and surface properties, that influence the interactions between inhaled minerals and living tissues and cells. Unfortunately, little attention has been given to the mineralogical aspects contributing to pathogenesis or to the development of occupational and environmental regulations for mineral particulates.

In this paper we present the basic mineralogical aspects of quartz and discuss how they relate to biological activity. Important underlying concepts of this discussion include mineral species and particles, structure, and composition. The major variables for predicting bioactivity are silica structure and metal ion impurities. Surface properties are also important in pathogenesis, and they have been reviewed in the mineralogy field (2, 3).

Mineral structures

One of the primary qualities of minerals is structure. Minerals exhibit translational periodicity (ie, their structures repeat over large atomic distances); therefore they are said to be crystalline. Noncrystalline or amorphous materials, such as glass, are not defined as minerals because their structures do not repeat in a regular fashion.

Silica is a chemical term for silicon dioxide (SiO₂). This general term describes a range of structures and properties. Silica can crystallize as one of at least eight polymorphs (α -quartz, β -quartz, cristobalite, tridymite, stishovite, coesite, moganite, and keatite),

each of which occurs in nature. (See reference 3 for illustrations of these polymorphs.) In addition, silica can occur in noncrystalline forms, and several amorphous materials are composed chiefly of silica with smaller amounts of other constituents (eg, water, cations, anions). Some of these polymorphs are not abundant. The diversity in structures exhibited by silica (including the structures of the rare polymorphs) must be exploited by future biological studies so that relationships between mineral structure and biological activity can be elucidated. Heaney & Banfield (3) provide a review of most of the structures of silica. It is critical for scientists to understand that silica does not refer to a single substance; therefore this term has limited utility for health studies or regulatory debates. Use of the more exact terms for the mineral species is essential in any discussion of biological activity or health effects.

Quartz. Numerous studies have demonstrated that samples of quartz can be biologically active, and under some conditions exposure to quartz appears to result in fibrosis or tumors or both (4—7).

Of the silica polymorphs, quartz is by far the most abundant because it is thermodynamically the most stable polymorph under ambient conditions. Quartz occurs in numerous rock types, soils, and beach sands, and quartz particles from these sources can be respirable. Quartz occurs as one of two polymorphs: α -quartz (or low quartz) and β -quartz (or high quartz). β -Quartz is stable only at temperatures above ~573°C, and it readily converts to α -quartz upon cooling.

The structure of α -quartz consists of corner-sharing tetrahedra linked to form double helices that coil along the c-axis. The cores of these helices form open, ditrigonal tunnels, which can accommodate extra cations in interstitial (nonframework) sites, as will be discussed later.

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Tridymite and cristobalite. The biological activities of tridymite and cristobalite have been studied extensively, and generally they appear to have activities comparable to quartz (5).

Tridymite and cristobalite are high-temperature, low-pressure polymorphs of silica. They form stably above $\sim 870^\circ\text{C}$ (tridymite) and $\sim 1470^\circ\text{C}$ (cristobalite) and metastably in some low-temperature environments. For example, these polymorphs often form during the devitrification of siliceous volcanic or synthetic glass. The tridymite $\rightarrow$ quartz and cristobalite $\rightarrow$ quartz transformations require the breaking of bonds. Hence even tridymite and cristobalite crystallized at high temperatures can remain metastable under ambient conditions. Tridymite and cristobalite occur as fine-grained crystals, often intimately intergrown with glass or other minerals, including each other.

Both the tridymite and cristobalite structures are based on polymerized sheets of tetrahedra (8), where the tetrahedra point alternately up and down. These sheets can be bonded by stacking in two ways. In one stacking scheme, alternate sheets are rotated by 60° or 180° to allow the joining of tetrahedra between the sheets producing tridymite. In the other stacking scheme, alternate sheets are shifted slightly, thus forming cristobalite. The similarities between these two structures allow them to intergrow extensively, and this type of intergrowth is referred to as a stacking defect (8).

Coesite and stishovite. The biological activities of coesite and stishovite have been studied much less than those of quartz, tridymite, and cristobalite (9–11). However, a few studies have indicated that these two silica polymorphs are much less biologically active and, in the case of stishovite, perhaps biologically inert.

Moganite and keatite. Two silica polymorphs (moganite and keatite) have structures similar to quartz. Consequently, the possibility exists that these polymorphs could intergrow with quartz on a fine scale, particularly in disordered silica samples. In fact, moganite has been reported in many natural, microcrystalline quartz specimens in concentrations ranging between 20 and 85% (12). Intergrowths of these polymorphs could significantly alter the properties of a quartz specimen, even if present in relatively minor amounts. The structure of moganite is similar to that of quartz (ie, tetrahedra are linked to form double helices that coil along the c-axis). Whereas in quartz each double-helix tube is linked to six others, in moganite each tube is only linked to four others.

Keatite has no demonstrated stability field. However, keatite can be synthesized over a range in pressure (350–1250 atmospheres) and temperatures (380 – 585°C). Keatite can appear as an intermediate phase during the hydrothermal crystallization of quartz (2), and it occurs with high altitude, atmospheric dusts (13) that are believed to originate from volcanic sources. Keatite has a structure similar in some respects to the structure of α -quartz. When viewed down the [110] axis, "double helices" are clearly visible in the keatite structure. However, some of the tetrahedra are shifted out of the double helices and into the ditrigonal tunnels. Thus one difference between keatite and quartz is that the ditrigonal tunnels are not continuous, which would affect the diffusion of cations into and out of the framework.

Noncrystalline silica. Synthetic and natural occurrences of noncrystalline silica are common. Most descriptions of silica glass address the nature of the short-range order, which can be probed using several techniques. Such studies suggest that silicon is dominantly in fourfold (tetrahedral) coordination with oxygen

(14). The relative abundances of coordination environments for silica at surfaces of glasses have not been reported; however, calculations of dissolution mechanisms for quartz in water have suggested that 5-coordinated silica surface sites are formed as intermediate steps. The nature of silica sites at the surface may affect biological activity in as much as it alters the charge density or distribution (ie, the proton donor-acceptor characteristics of oxygens in fivefold coordination with silica differ from those of oxygens in fourfold coordination).

Noncrystalline silica is less stable relative to the crystalline varieties. However, the transformation to a crystalline polymorph is generally sluggish because it requires the breaking of Si-O bonds. Transformation is often facilitated by the presence of H_2O . The relative instability of silica glass also results in higher solubilities, which in turn can result in lower biopersistence. However, no solubility data have been published to allow a comparison of the solubilities of crystalline and noncrystalline silica in physiological fluids.

Varietal types of silica. Some species of crystalline silica are described with varietal names — for example, chert, chalcedony, flint, and agate — and they consist predominantly of fine-grained α -quartz.

Stuffed derivatives. The stuffed derivatives constitute a group of minerals in which trivalent or divalent cations can substitute for some of the silica. This substitution creates a negative charge on the framework that can be compensated by a cation in an interstitial position. Eucryptite (LiAlSiO_4), nepheline ($\text{KNa}_3\text{Al}_4\text{Si}_4\text{O}_{16}$), and carnegieite (NaAlSiO_4) are examples of stuffed derivatives of quartz, tridymite, and cristobalite, respectively. By comparing the activities of the stuffed derivatives with those of their parent structures, one can isolate the biological effects specifically associated with these characteristics.

Mineral surfaces

Ultimately the surface cells of silica particles interact with cells. Some evidence suggests that quartz surfaces may be largely amorphous (15–16). Furthermore, most surfaces become protonated in air, particularly in aqueous environments. Nevertheless, for the silica polymorphs, the structure at the surface is influenced by the structure of the bulk material. Work by Fubini and her colleagues and by Shoemaker and his co-workers (in this volume) demonstrates that biological activity increases when silica surfaces are either heated or freshly fractured.

Chemical variability

Although the major chemical component of the silica polymorphs is silicon dioxide, other elements (principally cations) can be present in trace amounts. The four most important are aluminum, alkali cations, iron, and titanium. (See reference 2 for more details.) Aluminum readily substitutes for silica in a tetrahedral framework. In general, the transformation is coupled with the substitution of a monovalent cation into a vacancy site: $\text{Si}^{4+} + \square \rightarrow \text{Al}^{3+} + \text{X}^+$, where $\square$ represents a vacancy and X^+ is generally an alkali cation. Substitutions with divalent cations also occur: $2\text{Si}^{4+} + \square \rightarrow 2\text{Al}^{3+} + \text{Y}^{2+}$, where Y^{2+} is generally Ca^{2+} or Mg^{2+} . These substitutions occur frequently within numerous silicate mineral groups and account for most of the chemical variability in the feldspars and stuffed derivatives. Generally, aluminum is present in low amounts in the silica polymorphs (ie, $< \sim 10^{-3}$ wt%) (2). At

the other extreme, stuffed derivatives can contain aluminum substituted for up to one-half of the Si.

Alkali cations such as K^+ , H^+ , Li^+ , and Na^+ can occur in silica minerals to offset charge imbalances created by other substitutions (eg, the Si ~ Al substitution), but their concentrations are generally low (ie, <0.01 wt%) (2). These cations are generally too large to substitute for Si in the framework structure but instead occur in the open cavities within the framework.

Iron can be present in the silica polymorphs in amounts up to a few tenths of a weight percent. The presence and nature of iron may have a strong influence on the biological activity of a sample. Asbestos studies have suggested that mineral-derived iron can catalyze the production of oxygen radicals via a Fenton-type reaction ($Fe^{2+} \leftrightarrow Fe^{3+} + e^-$) (17–18). However, quartz contains significantly less iron than the amphibole asbestos minerals do.

Titanium can be present in silica polymorphs in amounts up to a few hundredths of a weight percent (2). However, the silica polymorphs typically accommodate much less titanium (<0.01 wt%), due to the relatively large size of the titanium atom compared with the size of the silicon atom. However, the substitution of titanium in silica polymorphs may have a minimal affect on the biological properties of quartz.

Linking mineralogical properties to biological activity

Structure, composition, surface periodicities, and dissolution properties of silica are among the factors likely to affect biological activity. Nolan et al (19) argued that the hydrogenated surface silanol groups are responsible for the hemolytic toxicity of the silica polymorphs. In support of this possibility, the activity of quartz can be diminished (19) by treating silica dusts with polyvinyl-pyrrolidone-N-oxide (PVPNO), a polymer that binds to proton donor sites.

Mineral species is clearly an important factor in determining biological activity, inasmuch as polymorphs vary in their cytotoxicity. It is relevant that regulatory distinctions are made between crystalline and noncrystalline silica. In fact, numerous researchers have noted differences in the biological activities of silica polymorphs (9–11). Variations in the biological activities of silica polymorphs may relate to structural differences. An additional complication arises from the possible presence of amorphous material on the surfaces of some specimens. For example, Min-U-Sil 5 (α -quartz) may have up to 10–15 wt% amorphous material on particle surfaces (15, 16), and the amount of amorphous material on a sample is affected by sample preparation (16). Future studies of biological activity must thoroughly characterize the nature of particulate surfaces of each sample.

Limited data on the biological activity of coesite and stishovite suggest that they are less active than quartz, cristobalite, or tridymite (9, 11). However, for at least some samples or assays, coesite appears to be as fibrogenic as quartz (10). Interestingly, most samples of rutile (structurally related to stishovite but with titanium in place of silicon) appear to be biologically inert in a variety of in vitro and in vivo assays (20), although at least one rutile sample is more cytotoxic than quartz (Saffiotti, National Cancer Institute, Bethesda, MD, personal communication).

Concluding remarks

Linking mineralogical properties with biological processes is an essential step in the understanding of the mechanisms underlying mineral-induced disease. Experiments can be constructed such

that the differences are exploited to allow mineralogical properties to be compared. For example, by comparing the biological responses of less well known polymorphs with quartz, one can assess differences in toxicity due to crystal structure. This type of approach leads to the recognition of mineralogical features that are important in pathogenesis, such as trace-element composition, specific surface periodicities, and freshness of fracture. Once these features are identified, the biological activity of a sample can be evaluated by determining their presence or abundance. From a practical perspective, this possibility could lead to procedures for neutralizing potentially hazardous samples by altering the specific properties that are pathogenic (eg, leaching a trace metal from the surface or binding a polymer to the active surface of the sample). From a risk perspective, the result may be an elimination of some mineral samples from lists of potentially hazardous minerals, a procedure which would lead to more rational regulations.

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