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Mineral–Fluid Interaction in the Lungs: Insights From Reaction-Path Modeling

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Thermodynamic modeling, in conjunction with available kinetic information, has been employed to investigate the fate of chrysotile and tremolite in the human lung. In particular, we focus on mineral–fluid reactions using techniques borrowed from geochemistry, including calculation of saturation indices, activity-ratio phase diagrams, and reaction-path modeling. Saturation index calculations show that fresh lung fluid is undersaturated with respect to both tremolite and chrysotile and these minerals should dissolve, in accordance with conclusions from previous work described in the literature. Modeling of reaction paths in both closed and open systems confirms previous suggestions that chrysotile dissolves faster than tremolite in lung fluid, which offers an explanation for the apparent increase in tremolite/chrysotile ratios in lungs of miners and millers over time. However, examination of activity-ratio phase diagrams and reaction-path model calculations raises the possibility not only that minerals dissolve congruently in lung fluid, but that secondary minerals such as talc or various Ca–Mg carbonates might potentially form in lung fluid as asbestiform minerals dissolve.

The health effects of asbestiform and related minerals have garnered significant attention in the past several decades. However, how these minerals evolve by reaction in the lung remains poorly understood. Most studies of the fate of minerals in the body concentrate on either dissolution/biodurability ("resistance to chemical dissolution in the body"; Jurinski & Rimstidt, 2001) or biopersistence ("a particle's total resistance to all clearance mechanisms"; Jurinski & Rimstidt, 2001). Generally speaking, most of the geochemical/mineralogical literature focuses on the dissolution (e.g., Bales & Morgan, 1985; Dove, 1999; Gronow, 1987; Luce et al., 1972; Mast & Drever, 1987; Parry, 1985; Thomassin et al., 1977) and the biodurability of various minerals important to human health (e.g., Hume & Rimstidt, 1992; Jurinski & Rimstidt, 2001; van Oss et al., 1999; Veblen & Wylie, 1993, and references therein; Werner et al., 1995; Ziegler et al., 2002). On the other hand, the medical literature tends to focus on the biopersistence of a mineral (e.g., Churg, 1993; Hesterberg & Hart, 2000; Moolgavkar et al., 2001; Searl et al., 1999; Zoitos et al., 1987). Each of these studies offers valuable information on the behavior of minerals in the lung, but none have addressed the possibility of in situ mineral transformation, that is, the conversion of one mineral to another.

Earth scientists have long recognized the occurrence of low-temperature mineral transformations in the near-surface environment during weathering and soil formation. Some weathering reactions can be represented by simple congruent dissolution. Take for example the dissolution of the minerals fluorite and quartz (see Table 1 for formulas of minerals discussed in this article):

$$\text{Fluorite} \leftrightarrow Ca^{2+} + 2F^{-} \quad [1]$$

$$\text{Quartz} + 2H_2O(l) \leftrightarrow H_4SiO_4{}^0 \quad [2]$$

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TABLE 1
Formulas of minerals discussed in the text

Mineral	Formula
Albite	$NaAlSi_3O_8$
Antigorite	$Mg_{48}Si_{34}O_{85}(OH)_{62}$
Calcite	$CaCO_3$
Chrysotile	$Mg_3Si_2O_5(OH)_4$
Diopside	$CaMgSi_2O_6$
Dolomite	$CaMg(CO_3)_2$
Fluorapatite	$Ca_5(PO_4)_3F$
Fluorite	CaF_2
Hydroxylapatite	$Ca_5(PO_4)_3OH$
Kaolinite	$Al_2Si_2O_5(OH)_4$
Magnesite	$MgCO_3$
Monticellite	$CaMgSiO_4$
Quartz (coesite, cristobalite, tridymite)	SiO_2
Talc	$Mg_3Si_4O_{10}(OH)_2$
Tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$
Wollastonite	$Ca_2Si_2O_6$

Here Ca^{2+}, F^-, and $H_4SiO_4{}^0$ are aqueous species, completely dissolved in water. Most studies of dissolution behavior or biodurability of minerals in the lungs have dealt with such congruent reactions, where it is assumed that no new solid phases are formed as the primary mineral dissolves. However, most weathering reactions involving silicate minerals in nature are incongruent dissolution reactions, in which only part of the mineral is dissolved, leaving a new (secondary) solid phase behind. For example, the dissolution of the mineral albite in the presence of dissolved CO_2 (carbonic acid) may be written:

$$2\text{Albite} + 2H_2CO_3{}^0 + 9H_2O(l) \leftrightarrow 2Na^+ + \text{kaolinite} + 2HCO_3^- + 4H_4SiO_4{}^0 \quad [3]$$

where Na and some Si are completely removed from the solid phase, and the secondary mineral kaolinite is left behind. Although such weathering reactions are somewhat slow, they do occur over time scales that overlap human life expectancy. For example, Krauskopf and Bird (1995) summarize data suggesting that the amount of time required to weather a 1-mm-diameter grain of fresh rock to kaolinite ranges from 20 to 250 yr, depending on the climate and the mineralogy of the parent rock. As mineral fibers and dusts in the lung have diameters on the order of 1 μm (i.e., three orders of magnitude smaller), and body temperature is higher than the 20–25°C to which the times just described refer, we can expect that at least some transformations of one mineral to another in the lung would occur on time scales well within human life spans.

The original impetus for this study was evidence reported by Churg (1993) that for humans exposed to asbestiform minerals over long periods of time, the ratio of tremolite to chrysotile in the lung is significantly higher than the tremolite/chrysotile ratio in the asbestos material to which they were exposed. The reason for this finding is subject to some debate. Churg (1993) reviews several explanations for this phenomenon, including more rapid dissolution of chrysotile than tremolite (cf. Hume & Rimstidt, 1992) and physical properties that make chrysotile more easily removed by macrophages (Churg et al., 1989). However, particularly intriguing in this regard is the observation of Wagner et al. (1987; quoted by Case, 1991) that tremolite asbestos was "clearly evident in the lungs of the rats after three months of exposure" in cases where no evidence of tremolite asbestos was found in initial and "respirable" chrysotile. The Wagner et al. (1987) observation, if valid, cannot be explained by either of the processes just noted, and led us to speculate about the possibility that chrysotile might be converted to tremolite in the lung. As we began to consider this question, it became apparent that the particular transformation of chrysotile to tremolite was highly unlikely in the human lung, for reasons that are considered later in this article. However, using geochemical modeling techniques, we found that transformations of chrysotile and/or tremolite to other minerals might be feasible. It should be noted that if such mineral transformations do occur in the human lung, then there are obvious, significant health ramifications. A mineral may be transformed naturally to a more or less harmful one, and in the long term it can be imagined that treatments might be developed to accelerate beneficial transformations. Although the focus of our study is on asbestiform chrysotile and tremolite, the idea of in situ mineral transformations has clear applications to the fate of all kinds of minerals in the lung.

APPROACH AND METHODOLOGY

Our approach is primarily based on equilibrium thermodynamics, although we do investigate the role of kinetics to the extent permitted by the availability of data on mineral dissolution and precipitation reaction rates and mechanisms. Even though kinetics may be important in controlling reaction rates, thermodynamics identifies the direction and eventual endpoint to which reactions will proceed spontaneously. All systems, including biological ones, are subject to the laws of thermodynamics. Living organisms can only alter the direction of a process as dictated by thermodynamics if they expend the energy required. This expenditure of energy will only occur if it confers some advantage toward the survival of the organism, such as maintenance, growth, reproduction, or detoxification. Thus, thermodynamics provides an important context for the fate of minerals in the lung, even if slow kinetics or vital effects prevent full attainment of an equilibrium state.

Another limitation of our approach is that, for the time being, we ignore the influence of organic components in lung fluid. This is again largely necessitated by the lack of most of the key thermodynamic and kinetic data required. There are several possible roles for organic components. Some may form aqueous complexes with metal ions and thereby increase mineral solubility. Organic components may also catalyze or inhibit

mineral dissolution and precipitation rates. Although organic components may play important roles in mediating mineral–fluid reactions, we do not believe that their inclusion in the modeling reported here, even if it were feasible, would change our major conclusions.

Saturation Indices

As a first step in our investigation, we determined saturation indices [SI = log (IAP/K)] for chrysotile and tremolite in a model lung fluid. The variable IAP is the ion activity product and K is the equilibrium constant for a given reaction. The IAP has the same form as the equilibrium constant, except that the actual activities rather than the equilibrium activities of reaction participants are used. Also, even though it is called the *ion* activity product, the activities of *all* species, including neutral aqueous species such as SiO_2(aq) and solid phases, must be included in the product. For example, for chrysotile, the dissolution reaction may be written as:

$$\text{Chrysotile} + 6H^+ \leftrightarrow 3Mg^{2+} + 2SiO_2(aq) + 5H_2O(l) \quad [4]$$

For which the IAP is

$$\text{IAP} = \frac{a^3_{Mg^{2+}} a^2_{SiO_2}}{a^6_{H^+}} \quad [5]$$

assuming the activities of pure solids and water are unity. For tremolite we write

$$\text{Tremolite} + 14H^+ \leftrightarrow 2Ca^{2+} + 5Mg^{2+} + 8SiO_2(aq) + 8H_2O \quad [6]$$

and

$$\text{IAP} = \frac{a^2_{Ca^{2+}} a^5_{Mg^{2+}} a^8_{SiO_2(aq)}}{a^{14}_{H^+}} \quad [7]$$

A mineral with a calculated SI < 0 should dissolve. A calculated SI > 0 implies a mineral should precipitate. Because the actual magnitude of the SI is dependent on reaction stoichiometry, and stoichiometries of reactions can differ widely, it is necessary to normalize or scale SI values in order to make meaningful comparisons between different reactions. This scaling can be accomplished using the expression (Wolery, 1979; Reed, 1998)

$$\text{SI}' = \frac{\log(\text{IAP}/K)}{\sum_i |\nu_i|} \quad [8]$$

where ν_i is the stoichiometric coefficient for each participant in the reaction.

The equilibrium constants at 37°C and 1 bar for reactions (4) and (6) were calculated using the SUPCRT92 software package (Johnson et al., 1992). To calculate the ion activity products (IAP) for each of these reactions, the activity coefficients for Ca^{2+} and Mg^{2+} were calculated using the Davies equation,

$$\log \gamma = -Az^2\left(\frac{\sqrt{I}}{1+\sqrt{I}} - 0.3I\right) \quad [9]$$

and γ_{SiO_2} was assumed to be 1 because SiO_2(aq) is uncharged. Mattson (1994; see also Kanapilly, 1977) reports that fibers in the deep lung would interact with the extracellular fluid that lines the lung. The pH of this fluid is ~7.4, and its composition is "regulated by rapid exchange with blood." Therefore, the ion concentrations used in these calculations are averaged from ion concentrations found in blood plasma. A similar procedure was followed by Hume and Rimstidt (1992). Average concentrations of Ca^{2+}, Mg^{2+}, and SiO_2(aq) in blood plasma are: Ca = 2.5×10^{-3} M, Mg = $1.25 \times 10^{-3} M$, Si = $1.5 \times 10^{-4} M$; the ionic strength of blood plasma = 0.12 M; and pH 4 under macrophage conditions, and pH 7.35 for blood plasma (Bell et al., 1972; Ganong, 1979; Green, 1972; Houssay et al., 1951; Hume & Rimstidt, 1992, and references therein).

The saturation index calculations provide important insights, but they do not allow for the possibility that some portions of the lung environment (e.g., inside a macrophage) may behave as at least a partially closed system. As chrysotile or tremolite dissolves in a partially closed system, concentrations of Ca, Mg, and Si could potentially build up and reach saturation levels. Also, the SI calculations just shown are limited to consideration of the stability of only one phase at a time. Therefore, we also have employed activity-ratio diagrams and reaction-path modeling to investigate possible mineral–fluid interactions.

Activity-Ratio Diagrams

Activity-ratio diagrams show the phase relations among many related minerals as a function of ion activities in aqueous solutions. As pointed out by Wood (1998), in order to construct such diagrams, it is necessary to place some constraint(s) on the system in order to be able to write unique chemical reactions among phases and to limit the number of variables considered. Common constraints are conservation of a system component (e.g., an element such as Al) in solid phases (i.e., assumption that a component is immobile) or assumption of constant volume. We have no reason to expect that all reactions among minerals in the lungs would take place under constant-volume conditions. Components that could be conserved within the solid phases are Si, Ca, and Mg. None of these components are strictly immobile. However, the least soluble of these components could be considered relatively immobile. According to the data in the previous section, the concentration of SiO_2(aq) in our model lung fluid is about an order of magnitude lower than that of Ca^{2+} or Mg^{2+}, implying a lower solubility of silica than of these alkaline earths. Thus, it seems reasonable to construct an activity-ratio diagram for the phases of interest assuming conservation of Si in the solid phases, which removes the activity of SiO_2(aq) as a variable. Then, the appropriate variables for plotting phase relations in the system Ca–Mg–Si–O–H become $a_{Ca^{2+}}/(a_{H^+})^2$ versus $a_{Mg^{2+}}/(a_{H^+})^2$. Ratios of ionic activities are employed in recognition of the requirement that all chemical reactions corresponding to phase boundaries on the diagram must be balanced with respect to charge. We constructed the activity-ratio diagram with the aid of the software package The Geochemist's

Workbench (Bethke, 1996) using one of the thermodynamic databases (thermo.com.v8.r6+.dat) included with the package. This database is based largely on the SUPCRT92 (Johnson et al., 1992) database used in the saturation index calculations.

Reaction-Path Modeling.

The activity-ratio diagrams just described do not take into account additional important inorganic components, such as carbonate, phosphate, sodium, and so on, that occur in blood plasma (and therefore presumably lung fluid). They also do not deal directly with kinetics or partially open behavior. Only reaction-path modeling can deal with the full complexity of lung-fluid/mineral systems. Reaction-path modeling treats the dissolution of primary minerals, with the possible attendant formation of secondary minerals, as a problem in irreversible mass transfer. The methodology was pioneered by Helgeson et al. (1969) and has since been applied to a wide variety of mineral–fluid interaction problems (e.g., Bethke, 1996; Reed, 1998). In this approach, primary minerals that are out of equilibrium with a fluid are reacted with that fluid in a stepwise manner. At each step, if the minerals are undersaturated in the fluid (i.e., SI < 0), then the primary minerals are either assumed to dissolve instantaneously, if no kinetic constraints are built into the model, or to dissolve at a rate defined by a specified rate law. Equilibrium thermodynamics are then employed to determine whether any secondary minerals have become saturated; if so, those minerals are allowed to precipitate until SI = 0 (precipitation kinetics can be built in also). Then the next step of the process is carried out and the procedure is repeated to some desired endpoint (e.g., complete dissolution of the desired mass of primary minerals, a set period of time, etc.). If the system is closed, and the steps are repeated a sufficient number of times, the fluid may reach saturation (equilibrium) with respect to the primary phases which can then no longer react. It is possible that one or more minerals may first appear and then disappear as the dissolution reaction progresses.

In our case, reaction-path calculations were facilitated using The Geochemist's Workbench (Bethke, 1996) with the database already mentioned. In order to do the reaction-path modeling calculations, it was necessary to specify a more complete composition for the model lung fluid (Table 2). In our case we based the model lung fluid composition on Gamble's solution, following Jurinski and Rimstidt (2001). The Ca and Mg concentrations in Table 2 are slightly lower than those in the average blood plasma concentrations used in the saturation index calculations, but the relatively small differences do not affect the major conclusions drawn from the calculations.

We carried out two different sets of reaction-path calculations. The first simulated a mostly open system and is referred to as a flush model. In the flush model, a fixed mass of minerals (cf. Table 3) was allowed to react with a fixed mass of the fluid (10 g H_2O plus the components given in Table 2) for a fixed period of time (1 day). After that period of time, the original packet of fluid was completely removed from the system and replaced by a fresh packet of solution of the same mass. The new packet of fluid was again allowed to react with the mineral assemblage for 1 day before it in turn was replaced with a fresh packet of fluid. This procedure was repeated for 18,250 days. Thus, the first model focuses on changes in the mineral assemblage as new fluid is flushed through the system on a daily basis for 50 yr. A flush model approaches a completely open-system model as the time for exchange of the fluid packet before it is replaced approaches zero. The second set of calculations simulated a completely closed system. In the closed-system model, a fixed mass of minerals (cf. Table 3) was allowed to react with a fixed mass of fluid (10 g H_2O plus the components given in Table 2) and the fluid was not replaced. In this system, changes to the mineral assemblages occur over time because the initial minerals do not dissolve instantaneously. The fluid composition evolves as the original minerals slowly dissolve and, in some cases, secondary minerals precipitate. The closed-system calculation was also carried out for 50 yr. These two models represent end-member cases. It is possible for a real process to fall somewhere between a totally open system (open to all components with constant renewal of fluid) and a totally closed one. In other words, the system could be open to some components but closed to others, or the fluid might be renewed only occasionally.

For both of the models, we assumed an initial mineral assemblage of quartz, chrysotile, and tremolite. We included quartz in the initial assemblage because of the ubiquity of quartz dust in the atmosphere (Norton & Gunter, 1999). Tremolite and chrysotile were assumed to be pure, end-member phases (no impurities or solid solution). The initial lengths and diameters of chrysotile and tremolite and the initial masses and specific surface areas of all three minerals are given in Table 3. The lengths, diameters, and masses of the tremolite and chrysotile fibers were selected based on information contained in Nayebzadeh et al. (2001) on asbestos fiber abundances and dimensions in lungs from miners and millers in Quebec. The surface areas of the fibers, required for kinetic modeling, were calculated geometrically from the selected lengths and diameters, assuming a cylindrical shape. In both sets of calculations, the rate constants for the

TABLE 2
Model lung fluid used for reaction-path modeling calculations

Component	Concentration (mol L^{-1})
Ca^{2+}	0.001735
Cl^-	0.115063
HCO_3^- [a]	0.03214
Mg^{2+}	0.001043
Na^+	0.144845
HPO_4^{2-}	0.001043
SO_4^{2-}	0.000556
SiO_2(aq)	0.00015

[a] Concentration of HCO_3^- adjusted at various pH values to maintain charge balance.

TABLE 3
Characteristics of initial minerals employed in reaction-path calculations

Mineral	Length (μm)	Diameter (μm)	Mass (g)	Surface area ($cm^2\ g^{-1}$)	Dissolution rate[a] ($mol\ cm^{-2}\ s^{-1}$)
Tremolite	3	0.3	7.6×10^{-4}	48280	1×10^{-16} (6.8) 5×10^{-16}(4.5)
Chrysotile	5	0.075	4.16×10^{-3}	212400	2.95×10^{-14}
Quartz	—	—	6×10^{-4}	600000	1.4×10^{-17}

[a]Tremolite: Nelson, Wood, and Gunter, in preparation; chrysotile: Hume and Rimstidt (1992); quartz: Rimstidt and Barnes (1980).

dissolution of the minerals quartz, tremolite and chrysotile were taken from the literature (Table 3). The kinetic model for dissolution reactions employed by The Geochemist's Workbench is expressed as:

$$\text{Rate} = A_S k_+ \left(1 - \frac{\text{IAP}}{K}\right) \quad [10]$$

where A_S is the total surface area (cm^2) of the mineral, k_+ is the rate constant ($mol\ cm^{-2}\ s^{-1}$), and IAP and K are the ion activity product and the equilibrium constant, respectively, for the dissolution reaction. The inclusion of the term $(1 - \text{IAP}/K)$ insures that the net rate of dissolution approaches zero as the solution approaches equilibrium saturation with the mineral in question. The precipitation of all minerals and the dissolution of minerals other than the starting phases (i.e., those that precipitated but then redissolved) were assumed to occur instantaneously, owing to insufficient information on the kinetics of these reactions. The precipitation of the chrysotile polymorph antigorite, silica polymorphs other than quartz (coesite, cristobalite, and tridymite), and chalcedony (cryptocrystalline quartz) was suppressed in all calculations. Calculations for both open and closed models were conducted at pH values of 4.5 and 6.8. The lower pH represents conditions within a macrophage whereas the higher value is closer to the pH of blood plasma. Calculations attempted at pH 7.35 did not converge under the conditions selected.

RESULTS

Saturation Indices of Chrysotile and Tremolite in Lung Fluids

The calculated scaled saturation indices are given in Table 4. Notice that, irrespective of pH, both chrysotile and tremolite are undersaturated in lung fluid. However, the degree of undersaturation decreases with increasing pH. Hume and Rimstidt (1992) and Parry (1985) arrived at the same conclusions with regard to chrysotile. If Mg^{2+} and Ca^{2+} are significantly complexed by organic components in lung fluid, then tremolite and chrysotile would be even more undersaturated than calculated here. Thus, in an open system where the lung fluid is renewed continually and therefore there is no accumulation of the products of dissolution, both chrysotile and tremolite should be unstable and dissolve. Consequently, in an open system, replacement of chrysotile by tremolite is thermodynamically impossible.

At a given pH, the scaled SI values are similar for the two minerals, indicating that the thermodynamic drive for dissolution is also similar. However, measured rates of dissolution appear to be 4–7 orders of magnitude greater for chrysotile (Hume & Rimstidt, 1992) than for tremolite (Mast & Drever, 1987; Nelson et al., in preparation) at equivalent temperatures, pH and fluid compositions. Thus, the hypothesis that the proportion of tremolite increases in the lung due to faster dissolution of chrysotile compared to tremolite remains viable, and is supported further by the reaction-path modeling reported later in this article.

Activity-Ratio Diagrams

Figure 1 presents an activity-ratio diagram plotting $a_{Ca^{2+}}/(a_{H^+})^2$ versus $a_{Mg^{2+}}/(a_{H^+})^2$ at lung conditions, 37°C and 1 bar, drawn assuming conservation of Si. In Figure 1, the thicker solid lines separate fields of stability of the various minerals in the system Ca–Mg–Si–O–H. The lines with the arrows denote the paths of the solution composition as progressively more chrysotile (A) or tremolite (B) reacts with a fixed mass of lung fluid in a closed system. Each new aliquot of added mineral is assumed to reach equilibrium immediately (i.e., without kinetic constraints). The start of the arrows shows the $a_{Ca^{2+}}/(a_{H^+})^2$ and $a_{Mg^{2+}}/(a_{H^+})^2$ values of lung fluid at pH 6.8.

Initially, the lung fluid in contact with chrysotile or tremolite would be undersaturated with respect to quartz. As either chrysotile or tremolite begins to dissolve in a closed system, the Si concentration in the fluid would increase until quartz saturation, at which point this mineral would be favored to

TABLE 4
Scaled saturation indices as a function of pH for chrysotile and tremolite in a model lung fluid with the following composition: $Ca = 2.5 \times 10^{-3} M$, $Mg = 1.25 \times 10^{-3} M$, $Si = 1.5 \times 10^{-4} M$, ionic strength = 0.12 M

Mineral	pH 4	pH 7.34
Chrysotile	−1.37	−0.19
Tremolite	−1.47	−0.23

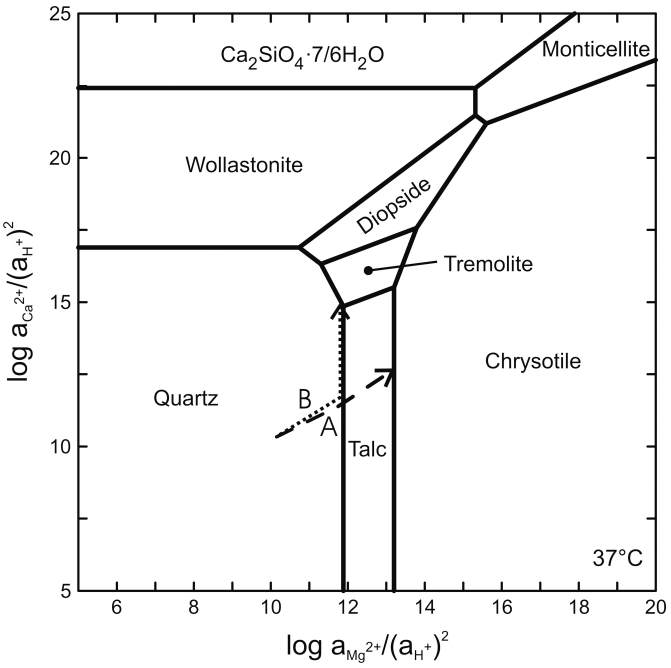


FIG. 1. An activity-ratio diagram, that is; a plot of log $a_{Ca^{2+}}/(a_{H^+})^2$ versus log $a_{Mg^{2+}}/(a_{H^+})^2$, for minerals in the system Ca–Mg–Si–O–H at 37°C. The dotted arrows show the reaction paths for closed-system dissolution of (A) chrysotile and (B) tremolite with no kinetic constraints. The arrow for tremolite has been offset slightly from the talc-quartz boundary for clarity. Both reaction paths start at a pH 6.8 and a composition as given in Table 3.

precipitate. However, owing to kinetic factors, quartz might not precipitate, and either the Si concentrations would build up until saturation with respect to amorphous silica, or the combined Mg and Si concentrations would build up to saturation with respect to talc. Whether or not saturation with respect to amorphous silica is reached, eventually continued dissolution of tremolite or chrysotile would lead to saturation with respect to talc. Thus, thermodynamics predicts that in a completely closed system with no kinetic constraints, either chrysotile or tremolite would dissolve incongruently to form talc. The paths taken from initial solution conditions to the talc field differ slightly for chrysotile and tremolite owing to the different stoichiometries of the dissolution reactions (4) and (6). The formation of talc from chrysotile may be kinetically easier to achieve, because both minerals are sheet silicates, whereas the transformation from a chain silicate (tremolite) to a sheet silicate may be more difficult.

After reaching the talc field, the reaction paths for continued dissolution of tremolite and chrysotile diverge markedly. The reaction path for chrysotile crosses the talc stability field until the fluid ultimately becomes saturated with respect to chrysotile, and the dissolution process ceases. On the other hand, the reaction path for tremolite follows the quartz (amorphous silica)–talc boundary until it intersects the tremolite stability field and the dissolution process once again ceases. Thus, the activity-ratio diagram suggests that in a closed system, quartz (amorphous silica) and talc should form as either chrysotile or tremolite dissolve in lung fluid.

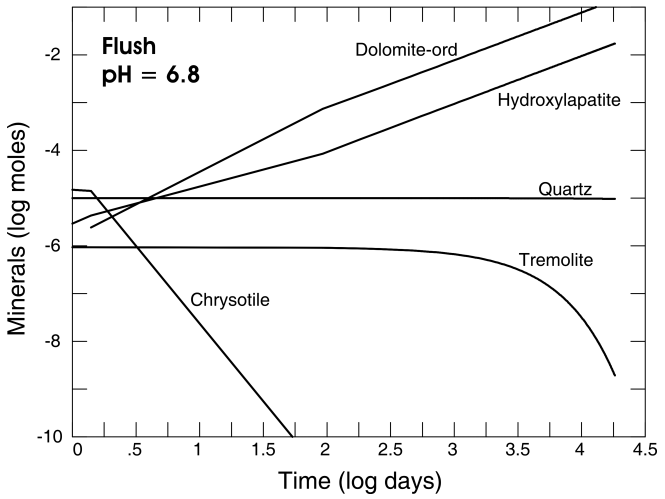
Based on the preceding discussion and examination of Figure 1, replacement of chrysotile by tremolite via reaction of lung fluid (with a blood plasma composition) with chrysotile requires the presence of an additional source of Ca. The additional source could be Ca-bearing minerals such as diopside, wollastonite, or calcite. However, such Ca-rich minerals are not universally associated with chrysotile, and do not appear to have been present in the chrysotile to which Wagner's rats were exposed. Thus, examination of the activity-ratio diagrams confirms the improbability of conversion of chrysotile to tremolite based on thermodynamic arguments alone.

Reaction-Path Modeling

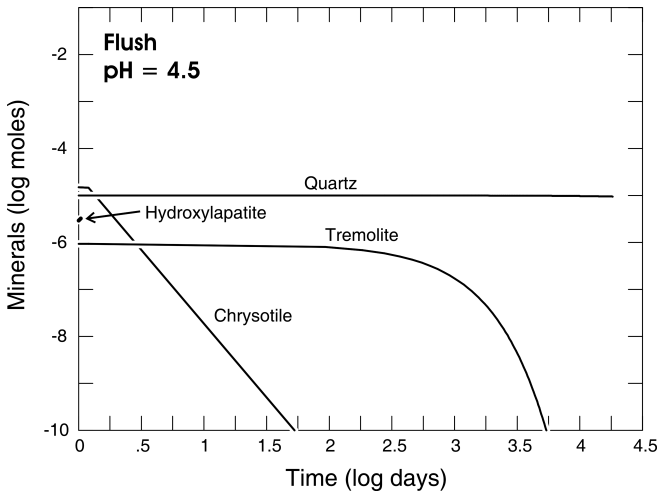
The results of the flush model calculations are shown in Figure 2. We first focus on the behavior of chrysotile and tremolite. At both pH 4.5 and 6.8, chrysotile persists only a few days before it starts to dissolve, and it is completely removed after about 50 days. There is little difference in the rate of disappearance of chrysotile between the two pH values for two reasons: (1) Hume and Rimstidt (1992) found that the rate of dissolution of chrysotile is independent of pH from 3.4 to 7.4, and therefore the rate constant is not a function of pH; and (2) chrysotile is sufficiently undersaturated at both pH values such that the $(1 - \mathrm{IAP}/K)$ term in Eq. (10) is nearly unity and does not effect the dissolution rate.

In contrast to chrysotile, tremolite persists to much longer times, only beginning to decrease in abundance significantly after 1000 days at pH 6.8 and 100 days at pH 4.5. Tremolite persists longer than chrysotile for several reasons. First, our (Nelson et al., in preparation) experimentally derived rate constants for the dissolution of tremolite are, depending on pH, approximately 60 to 300 times smaller than the pH-independent value for chrysotile. Second, the specific surface area of chrysotile was calculated to be a factor of 4.4 times larger than that of tremolite. Finally, the initial mass of the chrysotile is a factor of 5.5 greater than that of tremolite. The latter two differences result in a total surface area for chrysotile that is approximately 24 times greater than that of tremolite, contributing to the faster dissolution rate of chrysotile. However, sensitivity calculations show that when the total surface area of chrysotile is set at 100 times smaller than that of tremolite, chrysotile takes longer to completely dissolve, but it still dissolves faster than tremolite. These findings are consistent with the hypothesis that tremolite/chrysotile ratios in the lung increase with time due to more rapid dissolution of chrysotile relative to tremolite.

At both pH values, quartz does not dissolve significantly at any time during the 50 yr for which the reaction path was calculated. This is a result of the fact that the rate constant for quartz dissolution is at least an order of magnitude lower than that of tremolite, and the concentration of Si in blood plasma (our



(a)

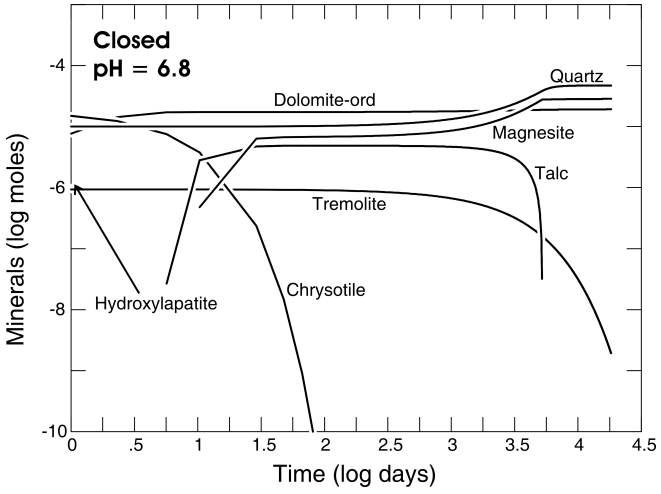


(b)

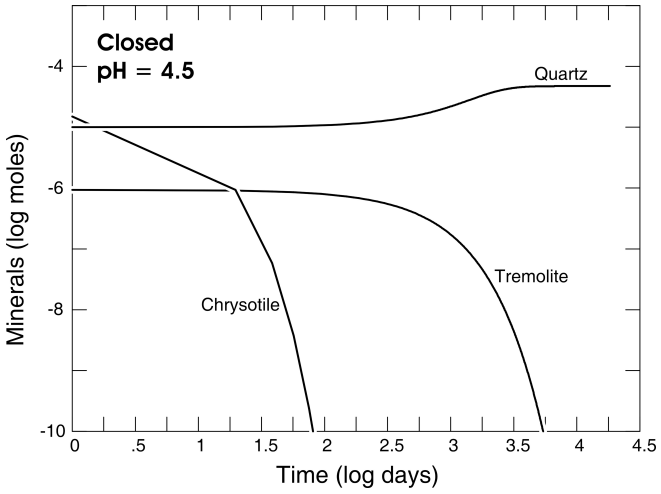
FIG. 2. Plot of the mass of minerals (log scale) versus time in an open system (flush) for the reaction of quartz, tremolite, and chrysotile with simulated lung fluid where the fluid (10 g water with constituents as in Table 2) is replaced on a daily basis. The initial pH of the fluid is: (a) 6.8 and (b) 4.5.

model for lung fluid) is relatively close to saturation with quartz, meaning that the $(1-\mathrm{IAP}/K)$ term in Eq. (10) is relatively small.

In the pH 6.8 open-system model, hydroxylapatite, although not present in the initial mineral assemblage, is predicted to precipitate during each flush step, resulting in a steady increase in hydroxylapatite contents with time. That blood plasma appears to be near saturation with respect to hydroxylapatite is not too surprising. If it were not near saturation, it would be difficult to maintain teeth and bones. However, at pH 4.5, such as might occur within a macrophage, hydroxylapatite is undersaturated and does not precipitate in the model. In fact, at the lower pH conditions, no secondary minerals whatsoever appear. On the other hand, at pH 6.8, ordered dolomite is predicted to become saturated after a couple of days and to continue to precipitate at every step along the reaction path. It is quite unlikely that dolomite would precipitate in the lungs because it is notoriously difficult to nucleate at low temperatures (Krauskopf & Bird, 1995; Drever, 1997; Langmuir, 1997). However, throughout the flush process calcite, although undersaturated, is close enough to saturation that slight increases in pH, Ca or carbonate concentration could cause it to precipitate. At the pH of blood plasma (7.35), calcite solubility will be lower than at pH 6.8, so precipitation of calcite is indeed possible. As is the case for dolomite, the rate of direct precipitation of hydroxylapatite is also slow (Krauskopf & Bird, 1995). Thus, it is possible that the appearance of this phase might be inhibited kinetically. It should also be noted that we have not included F^- in our model lung fluid. Its presence would open up the possibility of a fluorapatite component, which might further stabilize apatite.



(a)



(b)

FIG. 3. Plot of the mass of minerals (log scale) versus time in a closed system for the reaction of quartz, tremolite and chrysotile with simulated lung fluid with an initial H_2O mass of 10 g. The initial pH of the fluid is (a) 6.8 and (b) 4.5.

In the closed-system model, the results of which are shown in Figure 3, it is clear that tremolite persists for much longer times than chrysotile, as was the case in the open-system model. In the closed-system model, chrysotile initially does not disappear as rapidly as in the flush model, but it does disappear completely by 60 days. There is relatively little difference in the behavior of tremolite between the closed-system and flush models.

In the closed-system model at pH 6.8, hydroxylapatite appears at the very start of the model, but disappears completely very early. Ordered dolomite is predicted to form right at the start, increase in abundance slightly in the first several days, and then level off in abundance for the rest of the calculation. Quartz abundance stays fairly constant until after 1000 days, at which point it increases, and then plateaus at a higher level. This is in contrast to the flush model, where quartz abundance stayed constant for the duration of the calculation. The increase in quartz abundance in the closed system is due to the release of Si from the dissolution of tremolite and secondary talc. Quartz does not readily nucleate from a homogeneous aqueous solution, but if some quartz particles were already present in the mineral assemblage in the lungs, then growth of quartz on those original particles might be possible. Alternatively, rather than leading to the presence of quartz per se, the leaching of Ca and Mg during dissolution of minerals such as chrysotile, talc, and tremolite may leave an amorphous, silica-rich residue, which then dissolves more slowly. The dissolution rates quoted for tremolite and chrysotile are based on the rate of release of Si; leaching of at least some of the Ca and Mg from the structures of these minerals could occur well before the complete dissolution of the minerals (i.e., before the steep decreases in abundance shown in Figures 2 and 3).

Two minerals, talc and magnesite, appear in the closed-system model at pH 6.8 but do not appear in the flush model. One of these minerals, talc, also was predicted to form in a closed system based on the activity-ratio diagram. Talc does not appear until approximately day 5 of reaction, increases in abundance to a plateau, then decreases in abundance steeply after about 3200 days and finally disappears completely after 5000 days. It is interesting to note that talc appears at about the same time chrysotile starts to disappear, and begins to disappear itself once tremolite starts to disappear. This suggests that talc is largely formed as a replacement of chrysotile, but that the former is only stable as long as tremolite is present. In the closed-system model at pH 6.8, magnesite is predicted to start forming shortly after talc appears. Like talc, magnesite then rises to a plateau. However, unlike talc, the abundance of magnesite is predicted to increase again after several hundred days until it reaches a new plateau. Interestingly, after the abundance of magnesite reaches its first plateau, the curves for quartz and magnesite roughly parallel one another. As with dolomite, the rate of nucleation of magnesite may be too slow under lung conditions for it actually to precipitate in the lungs. However, talc precipitation may be facilitated by the similarity in crystal structure between chrysotile and talc.

The results of the closed-system model for pH 4.5 resemble closely those of the flush model at the same pH, except for some minor differences in the rates of disappearance of tremolite and especially chrysotile, and the increase in quartz abundance toward the end of the closed-system simulation. The results of reaction-path modeling illustrate why the reduction of pH within a macrophage is an effective strategy for removing harmful minerals. At pH 4.5, the rate of dissolution of tremolite is faster than at higher pH, but in addition, the formation of secondary minerals is suppressed effectively at the lower pH, with the exception of the predicted formation of some quartz in the completely closed system.

DISCUSSION

The calculations described here suggest the strong possibility that minerals in the lungs might not only dissolve congruently, but that incongruent dissolution or mineral replacement reactions might also take place over a human lifetime. Sensitivity analysis shows that the exact sequence of reactions and mineral products depends to a considerable extent on the relative mass proportions of initial minerals and fluid, the degree to which the system is open or closed, uncertainties in kinetic parameters (rate constants, surface areas), and variation in the fluid composition. Moreover, kinetic information was not included for any precipitation and many dissolution reactions, and the effects of organic constituents in the fluid, possible vital effects in macrophage cells, and the presence of other inorganic components in the minerals or lung fluid or both (e.g., Fe, F) were not considered. Finally, our calculations do not take into account the addition of minerals after the model processes have been initiated. Thus, it is currently premature to state with any degree of certainty that any *particular* mineral transformation should take place under lung conditions. However, the calculations presented here illustrate that reaction-path modeling has great potential for exploring mineral–fluid reactions in the lung, and this modeling will of course become more accurate as additional kinetic and thermodynamic information becomes available and is built into the models. Thus, our work should be seen as a starting point from which future improved models can be constructed, and our work points out the deficiencies in data that experiments can be designed to address. The most important conclusion to be drawn from our work is that although the specifics of mineral reactions predicted by our simplified models should be viewed with caution, the general idea that reactions in addition to simple congruent dissolution might occur in the lung is worthy of further investigation.

It is currently impossible to predict exactly how the results of the calculation would change had the calculations been carried out at pH 7.35 instead of 6.8, or had organic constituents been included in the calculations. However, the dominant effect of an increase in pH would likely be a decrease in the solubility of most of the minerals. For example, reactions (4) and (6) show that the solubilities of both tremolite and chrysotile

decrease with increased pH. Solubilities of carbonate minerals such as magnesite and dolomite also decrease with increasing pH. Decreased solubility means that more minerals might reach saturation, especially in partially closed systems, and that the rate of dissolution of minerals that do not reach saturation will decrease in accordance with Eq. (10). In general, each mineral has a different pH dependence, so an increase in pH will likely change the order of appearance and disappearance of minerals with time. On the other hand, one of the major effects of the presence of organic components would be to form aqueous complexes with some of the ions, such as Ca^{2+} and Mg^{2+}, that make up many of the minerals under discussion. The formation of such complexes would tend to increase the solubility of some of the minerals, counteracting to some extent the effects of increased pH. However, we emphasize again that the significance of our results is not that we are currently in a position to predict any specific mineral transformations. Rather, the significance is that mineral transformation of some kind might occur and should be taken into account.

Of the specific mineral transformation reactions discussed in this article; we feel there are two that are particularly worthy of further investigation. The first is the possible replacement of chrysotile by talc. If this occurs, and results in volume-for-volume replacement such that the original morphology of the chrysotile fibers is maintained (pseudomorphism), then it may be very difficult to distinguish talc-altered chrysotile from unaltered chrysotile by methods commonly employed to examine mineral fibers in lungs. Because talc and chrysotile have similar bulk chemical compositions (hydrated magnesium silicate), qualitative chemical analysis by scanning electron microscopic energy-dispersive spectroscopy (SEM-EDS) rarely would be conclusive. Similarly, if there is pseudomorphic replacement, then simple microscopic analysis would also be ambiguous because the morphology of the talc would be inherited from the parent chrysotile fiber. Thus, techniques sensitive to the internal crystal structure of minerals, such as x-ray diffraction (XRD) or transmission electron microscopy (TEM), would be required to detect transformation of chrysotile to talc definitively.

The second likely mineral transformation would be partial dissolution of chrysotile and/or tremolite whereby Mg and Ca are leached, leaving behind a Si-rich residue, possibly lacking long-range order. This residue most likely would dissolve eventually, but might possibly crystallize to quartz or other minerals if the fluid is not continually renewed.

It is interesting to note that none of the reaction-path calculations we carried out predicted the formation of tremolite from chrysotile or any other mineral. Thus, such a conversion appears to be thermodynamically impossible in the lung, whether the system is closed or not. There are also likely kinetic barriers to the nucleation of tremolite in the lung. Amphiboles (to which class tremolite belongs) have been found as a hydrothermal alteration product of pyroxenes (Boettcher, 1966, 1967; Meeker et al., 2003). However, the only reported successful syntheses of tremolite occur at much higher temperatures and pressures (Ahn et al., 1991; Jenkins & Hawthorne, 1995; Maresch et al., 1994; Pawley et al., 1993; Zimmerman et al., 1996) than those in the lungs, and we are unaware of any reports of the formation of tremolite in low-temperature geologic environments. Thus, both thermodynamic and kinetic constraints mitigate against the transformation of chrysotile to tremolite in the lung, and therefore the observations by Wagner et al. (1987) mentioned in the introduction remain unexplained.

CONCLUSIONS

Our model calculations confirm conclusions of previous studies that chrysotile and tremolite are undersaturated in model lung fluid and should dissolve, and that the rate of dissolution of chrysotile is orders of magnitude faster than that of tremolite. However, our study raises the possibility that minerals may not necessarily dissolve only congruently, leaving no trace of solid behind. Thermodynamic modeling suggests that minerals may also dissolve incongruently under certain circumstances, leaving behind residues of less soluble minerals, or they may be replaced by more stable minerals. Considerably more research needs to be carried out to verify whether the types of processes outlined here actually occur in vivo, and to make the models more realistic by incorporating organic components, more kinetic data, and so on. However, if these types of reactions do occur, they should have important ramifications for the fate of minerals in the human lung, and therefore for public health.

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