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Andrea Tannapfel
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Malignant Mesothelioma

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Preface

Malignant mesothelioma is a rare and aggressive tumor arising from the mesothelium. Pleural, peritoneal, and pericardial mesothelioma are possible entities according to the site of origin.

Diffuse malignant mesothelioma is strongly associated with exposure to asbestos and was first referred by Selikoff in 1965 as a “signal tumor” because of its close association with occupational and environmental exposure to asbestos.

There is a clear positive correlation between historical asbestos exposure and deaths caused by mesothelioma. Approximately, 2500 patients in the United States of America and 1000 patients in Germany annually are diagnosed with malignant mesothelioma. The incidence peak of mesothelioma will be reached in the next 10–20 years due to the extended latency period of about 30–40 years or more after exposure.

This issue of “Recent Results in Cancer Research” – Malignant Mesothelioma – is a comprehensive compilation of all topics related to asbestos and mesothelioma, written by well-known experts in their fields.

We intend to provide a broad overview of mineralogy of asbestos, analysis for lung tissue fiber content, and epidemiology of this disease.

The book also refers to all new diagnostic pathways like imaging, pathohistological as well as molecular approaches, genetic and molecular biological characteristics, and potential use of biomarkers for screening of mesothelioma.

Recent developments and novel approaches in surgery, chemotherapy, and radiotherapy of malignant mesothelioma are outlined by experts in this field.

The chapter about mineralogy of asbestos emphasizes the pivotal role of different physicochemical and biological features of chrysotile and amphibole asbestos for understanding the different hazards of exposure.

An outstanding team of international leading experts have contributed to this book. It is addressed to oncologists, radiologists, thoracic surgeons, pathologists, and pulmonologists with the intention to provide a scientific-based up-to-date view on mesothelioma research, diagnosis, and therapy strategies. A comprehensive understanding of all aspects of this disease will be the foundation to perform successful future laboratory research and clinical studies.

Andrea Tannapfel
Volker Neumann

Contents

Mineralogy of Asbestos

1

Thomas A. Sporn

Abstract The term asbestos collectively refers to a group of naturally occurring fibrous minerals which have been exploited in numerous commercial and industrial settings and applications dating to antiquity. Its myriad uses as a "miracle mineral" owe to its remarkable properties of extreme resistance to thermal and chemical breakdown, tensile strength, and fibrous habit which allows it to be spun and woven into textiles. Abundant in nature, it has been mined considerably, and in all continents save Antarctica. The nomenclature concerning asbestos and its related species is complex, owing to the interest held therein by scientific disciplines such as geology, mineralogy and medicine, as well as legal and regulatory authorities. As fibrous silicates, asbestos minerals are broadly classified into the *serpentine* (chrysotile) and *amphibole* (crocidolite, amosite, tremolite, anthophyllite, actinolite) groups, both of which may also contain allied but nonfibrous forms of similar or even identical chemical composition, nonpathogenic to humans. Recently, fibrous amphiboles, not historically classified or regulated as asbestos (winchite, richterite), have been implicated in the causation of serious disease due to their profusion as natural contaminants of vermiculite, a commercially useful and nonfibrous silicate mineral. Although generally grouped, classified, and regulated collectively as asbestos, the serpentine and amphibole groups have different geologic occurrences and, more importantly, significant differences in crystalline structures and chemical compositions. These in turn impart differences in fiber structure and dimension, as well as biopersistence, leading to marked differences in relative potency for causing disease in humans for the group of minerals known as asbestos.

1.1
Introduction and Historical Background

Minerals are naturally occurring, inorganic compounds of specific chemical composition and crystal structure. Their nomenclature typically stems as an honorific, to indicate a pertinent geographic area or to highlight a distinctive characteristic of the compound. Derived from the Greek asbestos ("unquenchable" or "indestructible"), asbestos is the collective term for a family of naturally occurring fibrous silicates that exist in metamorphic, altered basic, or ultra

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basic igneous rock. Asbestos and asbestiform minerals are narrowly defined and classified, as will be discussed below. The asbestos minerals have found much utility owing to their common properties of thermochemical and electrical resistance, high tensile strength, and flexibility. Insoluble in water and organic solvents, its fine fibers may be spun and woven into textiles and incorporated into many other types of materials, asbestos has seen literally thousands of industrial applications. The usage of asbestos dates, through fact and fable, to thousands of years ago. Once believed to have almost magical capabilities, first descriptions document its usage in the manufacture of pottery in Finland ca. 2500 BC. Additional historical attributions for early asbestos usage include cremation garments for royalty and for embalming the pharaohs of ancient Egypt, and the emperor Charlemagne reportedly astonished his guests at a feast by throwing table cloths made from asbestos into a fire from which the garments would be removed clean and unharmed. Medieval alchemists termed the mineral “salamander stone” referring to a mythical fireproof animal, and during these times asbestos was used in suits of armor [1]. Deposits of asbestos in the Ural Mountains led to the development of factories producing asbestos textiles in 1720. In the seventeenth century, fibrous minerals discovered in Germany termed Bergflachs or Bergleder likely contained amphibole asbestos, and by the mid-nineteenth century, some 20 asbestos mines were operating in Europe [19]. In colonial America, asbestos deposits were discovered in Pennsylvania and New England, where it was woven into textiles, and chrysotile was discovered in Quebec, Canada in 1860 [19]. Significant commercial usage of asbestos did not occur until the latter part of the nineteenth century, with the development of the demand for insulation for the burgeoning steam technology. At the turn of the twentieth century, additional applications for the useful minerals had been developed, deposits of amphibole asbestos species had been discovered in South Africa, and asbestos was once more being mined in the Urals, this time in large quantities. Commercial exploitation of asbestos was now global and full-blown, and by 1980 over 100 million tons of asbestos had been mined worldwide [19], accompanied by the development of serious health concerns related to its usage. It is the purpose of this chapter to describe what asbestos is from a mineralogic perspective, where it is to be found, and what are the important distinctions that allow relative differences within members of the asbestos group to have differing potencies on the basis of such differences in terms of inducing injury and producing disease following inhalation. It is well known from animal models that the oncogenic potential of fibrous dust increases following reductions in fiber diameter, and decreases with reduction in fiber length, and these considerations are generally more important than the chemical composition of the fibers themselves [5, 6, 16, 21]. The longer fibers have more potency to induce cell injury, proliferation, oxidant release, and inflammation. It is also the durability of the fibrous dust that confers biopersistence, and the potential to induce malignant disease following deposition of fibers in the peripheral airways and migration of fibers to the serosal membrane. Contemporary usage of asbestos has been curtailed following its wide recognition as a most dangerous substance; it is noteworthy that the health hazards of asbestos date to antiquity as well. Pliny the Elder cautioned against the purchase of quarry slaves from asbestos mines, noting that they tended to die young [1].

1.2
Geologic and Mineralogic Features

Asbestos is properly considered a commercial and legal rather than a mineralogic term for a group of fibrous silicate minerals with crystalline structure and by definition have lengths >5 μm and aspect (length: diameter) ratios of

3 or greater. In the USA, the nomenclature as defined by the Environmental Protection Agency encompasses six unique mineral species, conventionally divided into two distinct groups, the amphiboles and the serpentines [22]. Chrysotile is the sole member of the latter group, and as of the year 2000, accounted for virtually 100% of the asbestos used commercially. Historically, at least 90% of commercially used asbestos has been chrysotile. The amphibole group contains grunerite-cummingtonite (amosite, *vide infra)*, crocidolite (a fibrous variant of riebeckite), tremolite, actinolite, and anthophyllite. The name amosite is derived from the acronym AMOSA – Asbestos Mines of South Africa –giving reference to the company in the Transvaal Province of South Africa, the sole mine producing the mineral. As such, amosite, too, is a commercial, rather than a true mineralogic term, but by convention, amosite is used synonymously for the fibrous forms of grunerite-cummingtonite, just as crocidolite for the fibrous form of riebeckite. Among the amphiboles, only crocidolite and amosite have undergone significant commercial exploitation in industrialized countries, and collectively account for less than 10% of asbestos utilized in the last century. Large amounts of amosite were imported into the USA during World War II for usage in warship and merchant vessel insulation. The so-called noncommercial amphiboles, actinolite, tremolite, and anthophyllite, are common mineral species with wide distribution. They are relevant insofar as they are contaminants of other commercially useful mineral species such as talc and vermiculite, as well as chrysotile, and have been implicated in the induction of disease in humans. The asbestos minerals have nonpathogenic, nonasbestiform mineral counterparts of identical chemical composition. The noncommercial species of amphiboles all require the word “asbestos” after their mineral name for the purpose of distinguishing them from the nonasbestos forms. This is not necessary for crocidolite, amosite, and chrysotile as the nonasbestos forms have different names as discussed above (see Fig. 1.1).

Asbestos minerals owe their fibrous habit to the parallel growth of very fine and elongate crystals, producing bundles. The amphiboles may also occur as nonfibrous, chunky, acicular and shard-like forms. Nonfibrous serpentine minerals include antigorite and lizardite. The nonfibrous forms of both serpentine and amphibole minerals are more common and widespread than the asbestiform species.

Deposits of commercial asbestos are to be found in four types of rocks: the banded

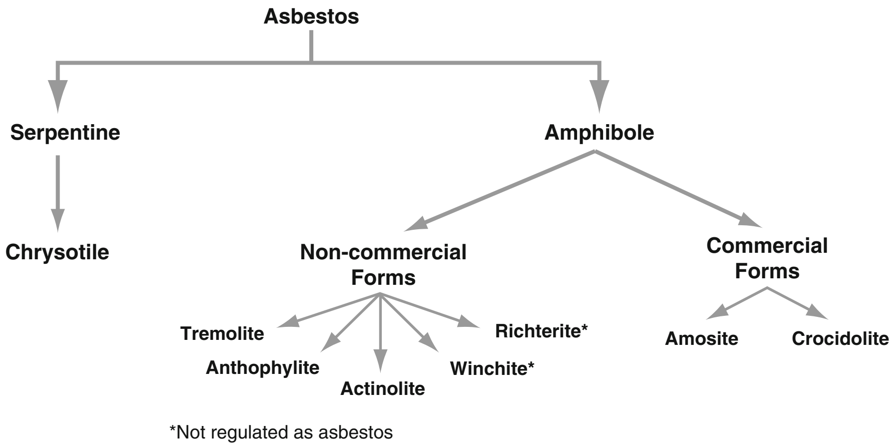


Fig. 1.1 Classification of asbestos and asbestiform silicates

ironstones, containing amosite and crocidolite; the alpine-type ultramafic rocks, containing chrysotile, anthophyllite, and tremolite; stratiform ultramafic inclusions, containing chrysotile and tremolite; and serpentinized limestone (chrysotile) [19].

1.3 Distribution and Physicochemical Properties of Chrysotile

Chrysotile is a common serpentine mineral with worldwide distribution, and the only one of this series mined as asbestos. The type 1 (alpine type, ultramafic rock) deposits are the most important sources of chrysotile asbestos, with principal localities occurring in the Ural Mountains of Russia and the Appalachian Mountains of the Canadian province of Quebec and the state of Vermont in the USA, as well as the state of California. Chrysotile has also been mined in the Italian Alps, Cypress, Zimbabwe, and the People's Republic of China [19] (Table 1.1). Commercially useful chrysotile is prepared from chrysotile ore in the milling process, with extracted long fiber chrysotile finding usage in textiles, and shorter fibers used in construction materials such as joint compound. Among the commercially exploited seams of the mineral, geographic variations are to be expected, both in terms of physical characteristics of the fibers, type, as well as proximity to fibrous species of noncommercial amphiboles. For example, the rich chrysotile ores quarried at the Coalinga, California yield fibers almost exclusively less than 5 µm [9]. There is also variance in the presence of other potentially dangerous minerals even within neighboring seams. McDonald et al attributed the difference in reported deaths due to mesothelioma among workers in several different mines within the province of Quebec to be attributable to local variances in the amount of tremolite contamination known to exist within the various mines [12]. The topic of chrysotile purity following milling, and the potential contamination by noncommercial species, is frequently argued in the ongoing asbestos litigation in the USA.

Table 1.1 Geographic distribution of asbestos species

Asbestos mineral	Geographic distribution
Chrysotile	Canada (Quebec), USA (Vermont, California), Russia, China
Crocidolite	South Africa (NW Cape Province, Transvaal), Western Australia
Amosite	South Africa
Tremolite	Turkey, Cyprus, Greece
Anthophyllite	Finland, USA
Actinolite	South Africa (Cape Province)
Winchite/Richterite[a]	USA (Montana)

[a]Asbestiform amphibole species, not classified as asbestos

Silicates may be classified on the basis of the polymerization type of the silicate ions and the variance in crystalline structure that occurs through association of various cations. Chrysotile is a hydrated (approximately 13% water as a crystal), phyllosilicate (sheet silicate) with chemical composition $Mg_3Si_2O_5\,(OH)_4$, containing the $(Si_2O_5)n^{-2}$ building block typical of the serpentine group of minerals [4] (Fig. 1.2). Whereas other serpentines and other layered silicates (clays, mica) form flat sheets, spatial imbalances between magnesium and silica ions within the tetrahedral and octahedral sheets of chrysotile cause the layers to roll to form concentric hollow cylinders. Chrysotile fibers will thus appear scroll-like when viewed end on (Fig. 1.3), containing a central capillary with 2–4.5 nm in diameter. The milling of chrysotile ore yields bundles of fibers of variable length, and some fibers may exceed 100 µm. The fibers may be curvilinear ("serpentine"), often with splayed ends due to the separation of fibers into individual and smaller fibrillar units (Fig. 1.4).

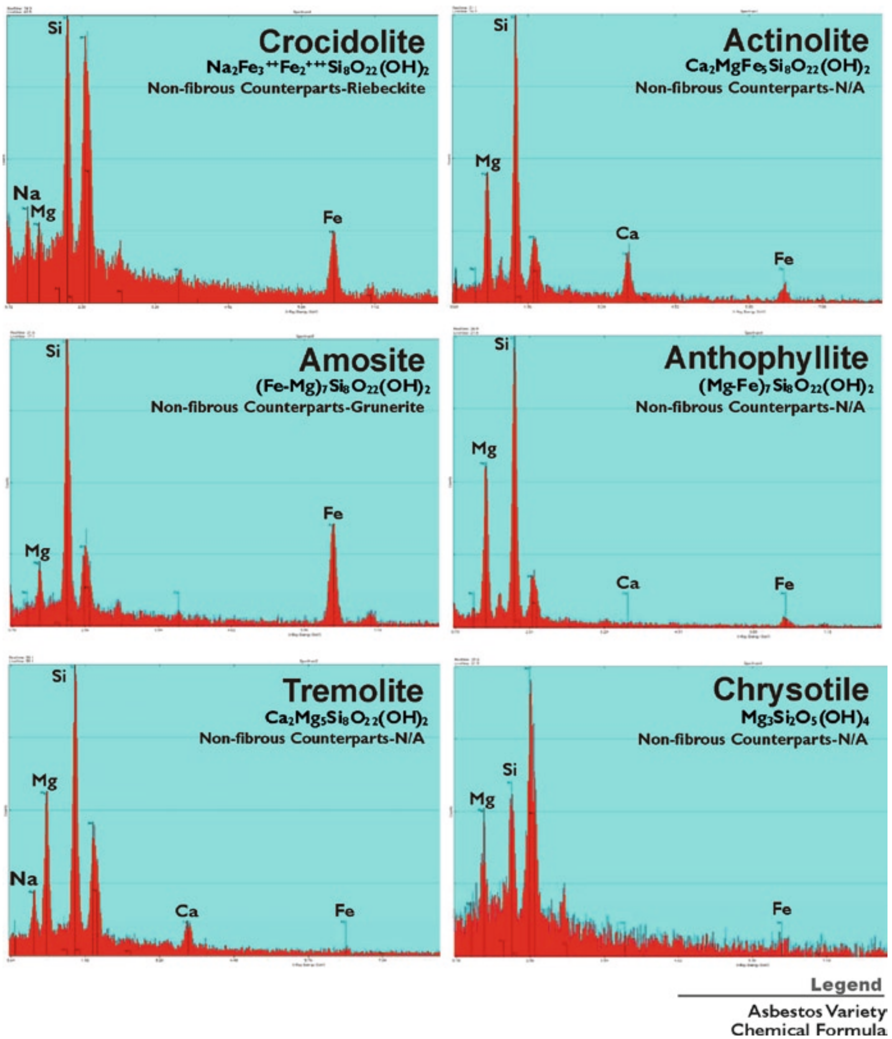


Fig. 1.2 Chemical composition and elemental spectra of asbestos

Some very long chrysotile fibers may be quite thin, but the diameter of chrysotile fibers tends to increase with increasing fiber length. Magnesium is an important constituent of both chrysotile and the amphiboles; the presence of soluble magnesium molecules on the outside of the curled chrysotile structure permits its leaching at the surface, facilitating the breakdown of fibers, within lung tissue, into successively smaller, fragile fibrils, which are then readily cleared from the body. Loss of magnesium changes the surface charge from positive to negative, which diminishes the oncogenic potential [16]. The clearance halftime of inhaled chrysotile within the lower respiratory tract is measured in only weeks, and may be much less. For example, with a clearance halftime measured in hours, the Calidria chrysotile from California is among

Fig. 1.3 Crystalline structure of chrysotile (Schematic diagram modified from [18])

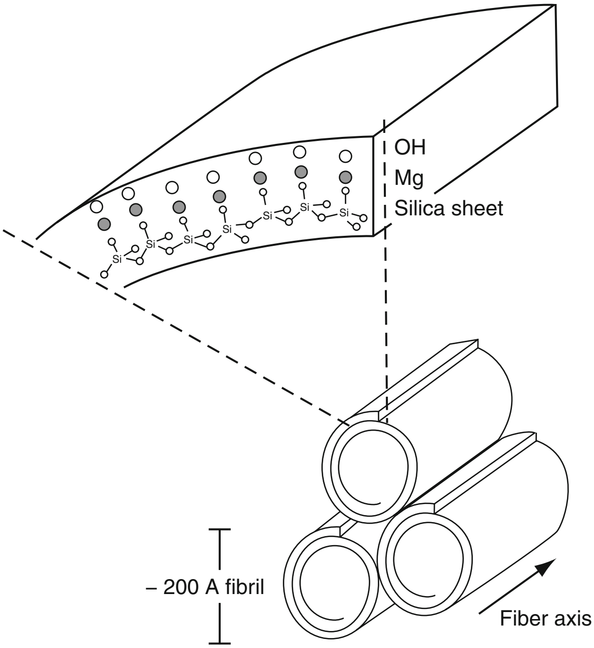
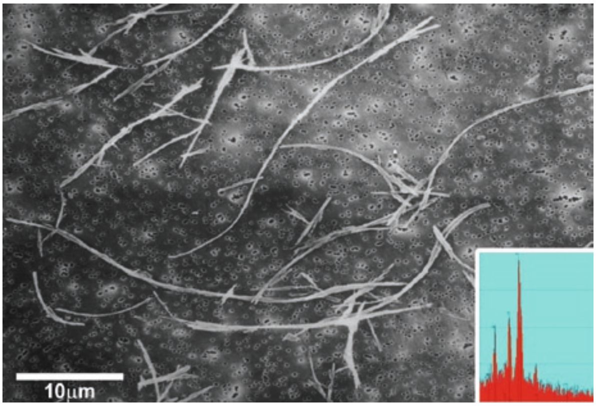


Fig. 1.4 Chrysotile asbestos fibers, scanning electron photomicrograph. Note long fibers of variable thickness and curvilinear "serpentine" morphology



the mineral fibers with the most rapid clearance from the lung. Other chrysotile may have biopersistence similar to the range reported for glass and stone wools [3]. Thermoresistant to a degree, 70% of the chrysotile structure is lost at 575°C, with complete loss of the structure occurring at 650°C [10]. Such high temperatures may be observed in the automotive braking process, causing pyrolysis and conversion to the nonfibrous, nonpathogenic silicate mineral forsterite [10]. Due to its physicochemical characteristics, chrysotile has a greatly reduced biopersistence in contrast to the amphibole species, and those features as described above provide a likely explanation for the reported reductions in oncogenicity for this species in humans in contrast to the amphiboles [2, 17], and for the epidemiologic studies that conclude that motor vehicle mechanics performing brake repair are not at increased risk for developing mesothelioma [8].

1.4
Distribution and Physicochemical Properties of the Amphibole Species

The amphibole asbestos minerals crocidolite, amosite, anthophyllite, tremolite, and actionolite are inosilicates, or chain silicates. Tremolite, actinolite, and anthophyllite are grouped together with chrysotile as "white asbestos" and classified under the United Nations chemical identification schema as UN2590. Amosite "brown asbestos" and crocidolite "blue asbestos" are classified as UN2212. Amphiboles typically occur when veins of the mineral are created when cracks form in rocks during movement of the earth. These conditions help provide the environment necessary for massive amphibole crystallization and transformation to the fibrous form. The amphibole minerals are common, but their occurrence as exploitable forms is limited to certain locations where they obtain the proper physicochemical characteristics and abundance to be used as commercial asbestos. The major deposits of commercial amphiboles have generally been limited to the banded ironstones of Western Australia and the Transvaal and Cape Provinces of South Africa. Alpine-type and stratiform ultramafic rock are sources of chrysotile, as well as the noncommercial amphiboles tremolite, actinolite, and anthophyllite, the major source for the latter occurring in Finland with smaller deposits in rocky outcrops of the USA [19]. Another source of asbestiform amphiboles is to be found in the area around Libby, Montana, USA. Libby is the site of the largest mined deposit of vermiculite in the world, and the alkaline-ultramafic rock is rich in amphiboles, chiefly richterite and winchite (sodic-calcic tremolite), all of which can exist in asbestiform or fibrous habit [15, 23]. The latter species are not listed in the US Federal Regulations governing asbestos, but their recognition is important in view of the abnormally high number of asbestos-related diseases and deaths in former vermiculite miners and millers and residents of this area, and the potency of the Libby amphibole in terms of inducing mesothelioma is reported to be similar to crocidolite [7, 13, 14]. Anthophyllite, tremolite, and actinolite are common constituents of the earth's crust, but have not been exploited commercially in industrialized countries, and are frequently associated with serpentine minerals, vermiculite, and talc. The noncommercial amphiboles may assume a variety of forms, including nonfibrous forms.

The chemical and crystalline structures of the amphiboles are highly similar, and generally may be distinguished only on the basis of chemical composition, and in specific the cation constituents (Fig. 1.2). Crystalline amphibole minerals demonstrate perfect prismatic cleavage, with direction of the cleavage parallel to the length of the silicate chains [20]. The silicate chains are formed by linear arrays of SiO4 tetrahedra linked by octagonal groups of cations, and may be of significant length (Fig. 1.5). The crystalline amphibole fibers are substantially more brittle than chrysotile, limiting their potential for fabrication. These mineralogic attributes confer the potential for great fiber length, and accordingly, significant pathogenicity following deposition in the lung (Figs. 1.6–1.9). As their straight, broad fibers are resistant to fiber fragmentation and chemical degradation in the body, the biopersistence of the amphiboles is much greater than chrysotile, and their clearance halftime is generally measured in decades. The crystalline structure of the amphiboles also contains less water than chrysotile, and there is greater resistance to pyrolysis. Amphibole fibers are less flexible than chrysotile, permitting greater friability with potential to release respirable particles.