This student paper was written as an assignment in the graduate course

Free Radicals in Biology and Medicine

(77:222, Spring 2001)

offered by the

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The University of Iowa
Iowa City, IA 52242-1181
Spring 2001 Term

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Asbestos: A Particular Matter

by

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For 77: 222, Spring 2001
2. April 2001

Abbreviations:
ESR (electron spin resonance, also known as electron pair resonance)
ROS (reactive oxygen species)
RNS (reactive nitrogen species)

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Abstract

Asbestos is a group of fibrous particulates with iron complexed in silica. Asbestos can be viewed both from its role as a xenobiotic protagonist and as a model for the study of mechanisms and pathways involved with other initiators of chronic inflammatory lesions and cancer. The highly reactive free radical species and iron in its role as a catalyst are considered to be central in the mechanism of asbestos mediated tissue pathogenesis. The following report will cover primary properties and mechanisms of asbestos related to its toxicity.

Introduction

Asbestos has been a widely used commerial product in the United States and elsewhere for many years. Beginning in the early 1900's, millions of tons of asbestos were mined, processed, and consumed in the United States alone [5]. Asbestos is considered to be an industrial chemical [3] and has been primarily used as an insulator in construction. The new use and production of asbestos is almost nonexistent in the United States, however, there are still many public and private buildings with asbestos components.

Asbestos becomes a significant biological hazard when people are exposed to the inhalation of airborne asbestos dust particles [3]. The time between exposure and the appearance of significant clinical symptoms associated with toxicity can range from 15-40 years and is dependant upon the amount of exposure [5]. Progressive pulmonary fibrosis (asbestosis), pleural disease (effusion and pleural plaques), bronchogenic carcinoma, and malignant mesothelioma are all considered to be caused by asbestos [5]. These diseases all originate within the respiratory system and involve the loss of lung tissue function.

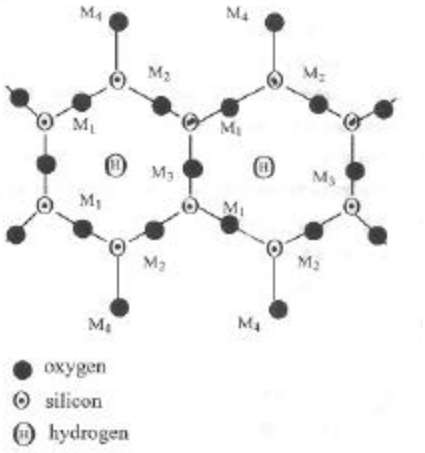
Structural, Molecular, and Cellular Aspects

The term asbestos refers to two classes of crystalline fibres (serpintine and amphibole) primarily composed of silica (SiO_2) [3,5]. Asbestos has also been described as a group of hydrated silicates (salts of silicic acids) with a greater than 3:1 (length:diameter) ratio [7], although the amphibole class does not always appear with a hydrated formula in the literature [3]. This may be significant when making comparisons

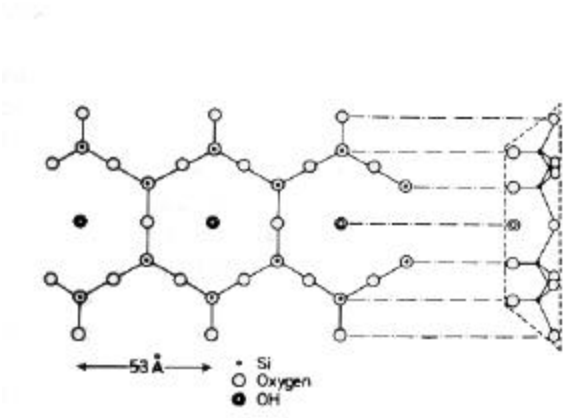
between *in vivo* and *in vitro* data. Greater than 95% of asbestos utilization is derived from the chrysotile ($3MgO \cdot 2SiO_2 \cdot 2H_2O = Mg_3Si_2O_5[OH]_4$) variety of the curly-shaped serpintine class[5]. The straight rod-shaped amphibole class includes crocidolite ($Na_2O \cdot Fe_2O_3 \cdot 3FeO \cdot 8SiO_2$ also seen as $Na_2[Fe^{3+}]_2[Fe^{2+}]^3Si_8O_{22}[OH]_2$), amosite ($[Fe,Mg]_7Si_8O_{22}[OH]_2$), and tremolite [5]. More varieties exist in both classes.

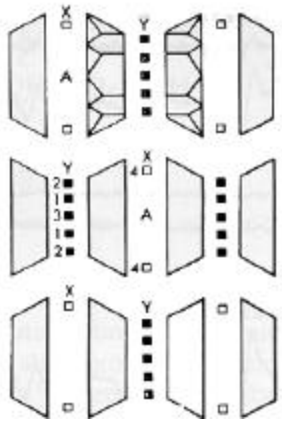
Figure 1. Schematic structural presentations of the crocidolite variety of amphibole (A) including cations as $M_{1\text{-}4}$ [2]. In crocidolite and amosite these cations are 26-36% iron by weight [6]. In tremolite they are 0-1% iron by weight [6]. A general amphibole is also shown (B) including cations as X, Y, and A in the end view of the rod-like chrystalline structure [2]. A schematic of the chrysotile variety of serpentine is shown between the dotted lines in (C), with cylindrical (D), and spiral (E) fibres illustrations[2]. Iron appears as 0-3% by weight in chrysoltile [6]. While other metal cations appear within the asbestos crystalline structure, the iron rich crocidolite and amosite have been shown to be the most carcinogenic to humans [6].

(A) [2]

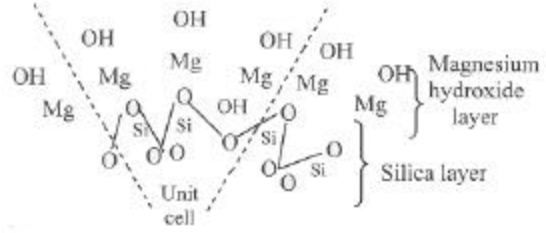


(B) [4]





(C) [2] (D) [2] (E) [2]



As a genotoxic substance, asbestos may cause disease on the molecular level through DNA damage, abnormal alteration of gene transcription, and the disruption of normal protein expression [5]. Cell cycle activity and inflammation can be affected through these changes [5], and it is known that these abnormal alterations are related to cancer induction. Additionally, chronic inflammation may lead to, but not be necessary for, the induction of cancer.

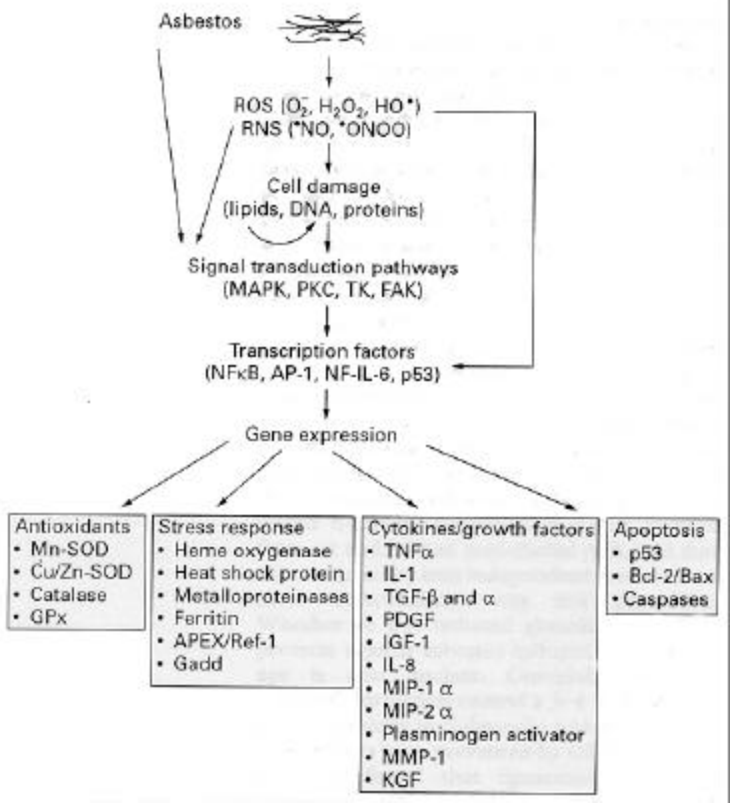


Figure 2 [5]. Molecular pathways of pulmonary tissue damage are illustrated [5]. Asbestos has been shown to initiate this damage through the iron catalyzed initiation and propagation of free radical ROS, the production of RNS, and the additional possibility of other mediators [5]. The following are abbreviations and formulas used in the figure: $O_2^{\cdot -}$ (superoxide), H_2O_2 (hydrogen peroxide), $HO^{\cdot}$ (hydroxyl radical), $^{\cdot}NO$ (nitric oxide), $^{\cdot}ONOO$ (peroxynitrite), DNA (deoxyribonucleic acid), and kinases (MAPK, PKC, TK, and FAK) [5].

Free radical formation occurs both with and without phagocytic cell involvement [4] and may be a primary biochemical mechanism in the onset of asbestos associated diseases. Macrophage involvement causes abnormal protease release within cells that have engulfed silica and asbestos particles, and can eventually lead to cell death [3]. When cell death occurs, both proteases and asbestos particles are released to produce further damage [3]. During chronic inflammation macrophages produce ROS, RNS, and secrete hydrolytic enzymes linked to tissue damage [3]. The cell free formation of ROS from iron-asbestos complexes and oxygen will be covered in the biochemical reactivity section of this report.

Biochemical Reactivity: The Importance of Iron and Reactive Oxygen Species

Two primary initiating biochemical mechanisms are now known to exist in the pathogenesis of asbestos toxicity and both include the formation of ROS [5]:

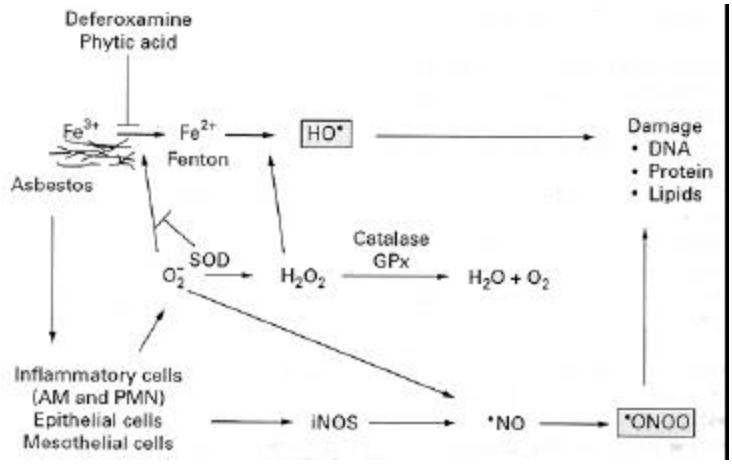


Figure 3 [5]. Proposed free radical mechanisms of pathogenesis due to asbestos exposure. Portions of this model have been shown to occur, however, the relative significance of different pathways is not known [5]. Previously unmentioned definitions in this figure include: SOD (superoxide dismutase), GPx (glutathione peroxidase), catalase (CAT), iNOS (inducible nitric oxide synthetase), AM (alveolar macrophages), and PMN (neutrophils) [5].

The literature as a whole has favored investigations of radical production via the Fenton reaction (1), at least partially due to experiments performed under non-cellular

conditions. Recent experiments have indicated the possibility that the oxidation of Fe^{3+} in the presence of oxygen di-radical (2) may be the prominent reaction driving intracellular ROS and RNS formation [2,8]:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO^{\cdot} \qquad (1)$$

$$Fe^{2+} + O_2 \rightarrow Fe^{3+} + O_2^{\cdot -} \qquad (2)$$

Reaction (2) is favored under concentration ratios of hydrogen peroxide and oxygen approaching physiological conditions ($[O_2]/[H_2O_2]$ greater than or equal to 1000) [8]. The actual experimental findings showed that the Fenton reaction is favored at $[O_2]/[H_2O_2] < 10$ and reaction (2) is favored at $[O_2]/[H_2O_2]$ greater than or equal to 100 [8]. Multiple regulatory mechanisms can be seen to occur in the pathways following reaction (2). Although many of the primary reactions involved are known, the changes brought about via chronic inflammation and carcinogenesis are not well understood. One reaction not shown in figure 3 is lipid peroxidation (3), one of the immediate effects of ROS production, causes membrane damage in cells[5]:

$$Fe^{2+} + ROOH \rightarrow Fe^{3+} + HO^- + RO^{\cdot} \qquad (3)$$

SOD, CAT, and GPx are three important enzymes shown to protect against too much oxidative stress in normal cells (figure 3). Their regulatory protection is unbalanced and overwhelmed during asbestos induced disease processes.

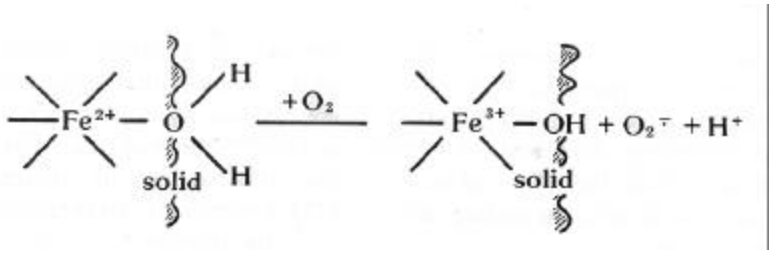
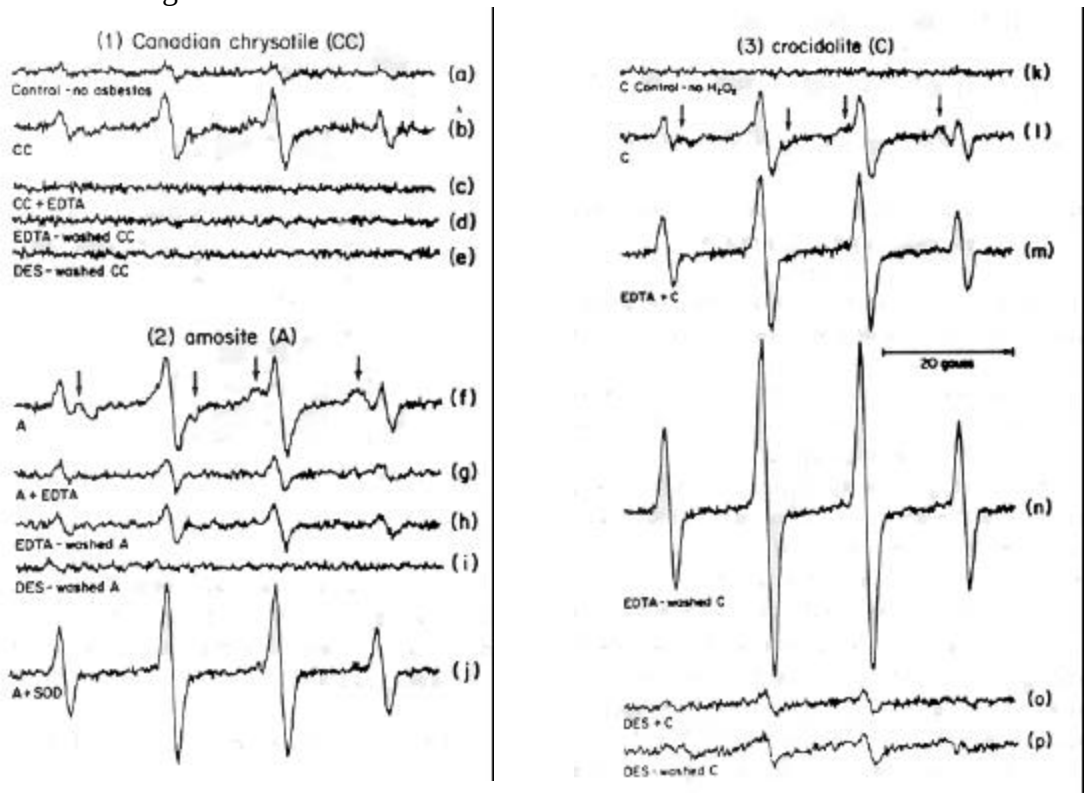


Figure 3 [4]. Proposed mechanism of surface superoxide production on asbestos fibres [4].

Radical production has been verified through ESR experimental designs such as the following one in figure 4:

Figure 4 [4]: Direct extracelluar evidence of free radical formation upon the exposure of iron containing asbestos to an oxidative environment.



Equivalent concentrations of hydrogen peroxide were added to 1mg/mL of Canadian chrysotil (CC), amosite (A), and crocidolite (C) respectively [4]. It is interesting to note that only oxygen would need to be provided to cells, since all hydrogen peroxide in cells comes from di-oxygen via superoxide. Controls were done (a and k) to insure that the peaks were not due to artifact or the background presence of hydroxyl radical [4]. The four distinct spikes of hydroxyl radical are overlapped by superoxide (f and l) where the arrows are located, and this is confirmed by their disappearance upon the addition of

SOD whose only known target is superoxide.[4]. The iron chealation of the ferric form of iron by DES (desferrioxamine) blocks its reduction by superoxide and halts the completion of the Haber Weiss reaction (5) where iron is reduced in a non-cellular environment as shown by equation (4). This is the opposite of equation (2) where the reaction is controlled by an environment more closely resembling a cellular milieu.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO^{\cdot} \qquad (1)$$

$$Fe^{3+} + O_2^{\cdot -} \rightarrow Fe^{2+} + O_2 \qquad (4)$$

$$O_2^{\cdot -} + H_2O_2 \rightarrow O_2 + HO^- + HO^{\cdot} \qquad (5)$$

The chealation of iron can cause the reduction of catalytic hydroxyl generation (as above with desferrioxamine) by blocking all of irons coordination sites, or increase the catalytic generation of the hydroxyl radical (as with EDTA) by leaving sites open as can been seen in figure 4 [4].

Summary

While the scientific study of asbestos has been extensive, the relationships between asbestos toxicity and all its mechanisms of action are not definitive. Current and future knowledge related to the xenobiotic nature of asbestos will not be limited to the implementation of protection from asbestos and the treatment of asbestos mediated diseases. This information can be utilized as a model for dealing with many other disease states where the mechanisms involved in oxidative stress and the iron-mediated formation of reactive oxygen species play a potentially significant role in pathogenesis.

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