
REVIEW

REVIEW OF THE DIFFERENCES BETWEEN CHRYSOTILE AND AMPHIBOLE ASBESTOS

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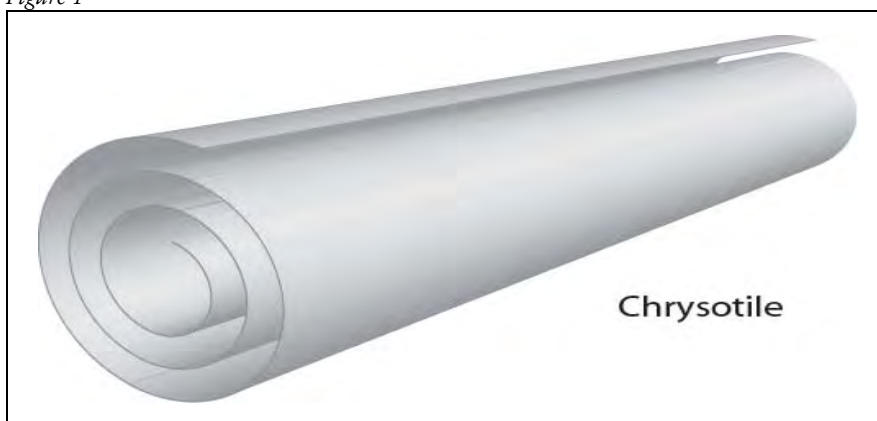
'Asbestos' is not a mineral in itself. It is a collective term given to a group of minerals whose crystals occur in fibrous forms. The term 'asbestos' was adopted for commercial identification.

The six minerals commonly referred to as asbestos come from two distinct groups of minerals. One group is known as serpentines (chrysotile, white asbestos); while the other group is the amphiboles (amosite, brown asbestos; crocidolite, blue asbestos; anthophyllite; tremolite; and actinolite). While both are all silicate minerals, the two groups are chemically and mineralogically distinct.

CHRYSOTILE

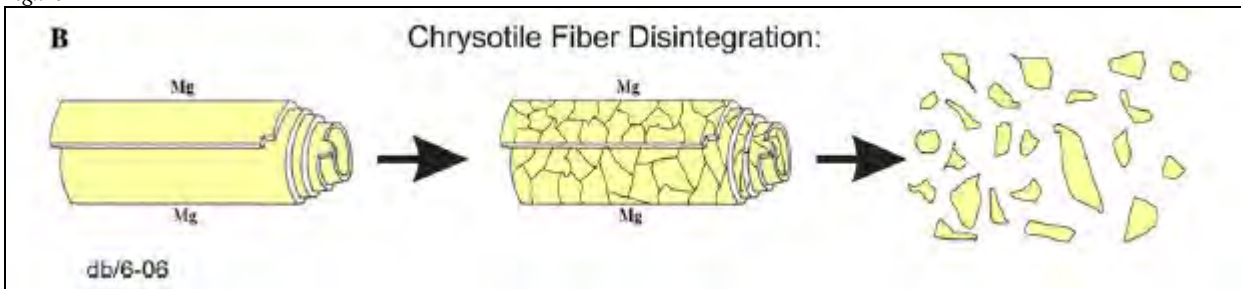
Chrysotile is a sheet silicate which is formed as a very thin rolled sheet as illustrated in Figure 1. The sheet is about 8 angstroms thick (0.8 nanometers thick). It is composed of a sandwich of magnesium and silica. In the lung, the acid environment of the macrophage scavenger cell quickly breaks apart the sheet structure causing the fiber to decompose into small pieces (Figure 2). These pieces can then be readily cleared from the lung. If the fiber is swallowed and ingested it is attacked by the even stronger acid environment (hydrochloric acid, pH 2) in the stomach.

Figure 1



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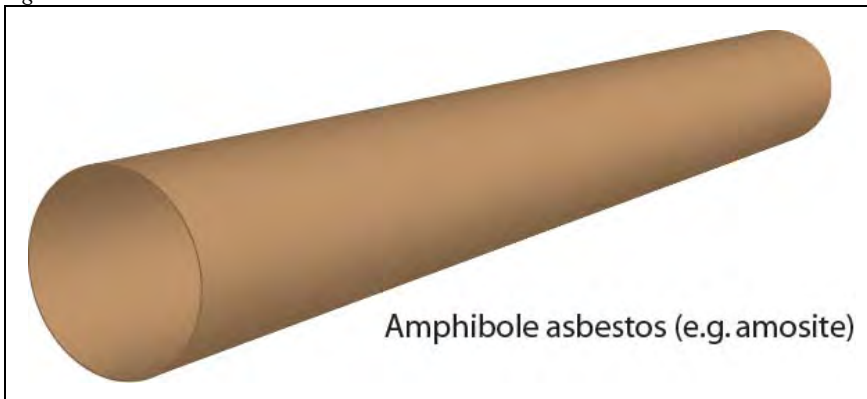
Figure 2



AMPHIBOLE ASBESTOS:

This is in contrast to the amphibole asbestos fibers which are formed as solid rods/fibers as illustrated in Figure 3. The structure of an amphibole is a double chain of silicate tetrahedral which makes it very strong and durable. The external surface of the crystal structures of the amphiboles is quartz-like, and has the chemical resistance of quartz. The amphibole fibers have negligible solubility at any pH that might be encountered.

Figure 3



THE KEY FACTORS THAT DETERMINE FIBER TOXICITY:

Mineral fiber toxicology has been associated with three key factors:

- DOSE,
- DIMENSION AND
- DURABILITY.

DOSE:

The dose is determined by the fiber's physical characteristics/dimensions, how the fibrous material is used and the control procedures that are implemented. In addition, the thinner and shorter fibers will weigh less and thus can remain suspended in the air longer than thicker and longer fibers. Most asbestos fibers are thinner than commercial insulation fibers, however, they are thicker than the new nano-fibers which are currently being developed.

DIMENSIONS:

The fiber dimensions govern two factors, that of whether the fiber is respirable and secondly if it is respirable the dimensions are also a factor in determining their response in the lung milieu once inhaled. Shorter fibres of the size which can be fully engulfed by the macrophage will be cleared by mechanisms similar to those for non-fibrous particles. These include clearance through the lymphatics and macrophage phagocytosis and clearance. It is only the longer fibers which the macrophage can not fully engulf which if they are persistent can lead to disease.

The importance of fiber length in asbestos toxicity was first addressed in studies by Vorwald et al. (1951). Subsequently, dose, dimension and durability have been shown to be important determinants for synthetic mineral fibers (Hesterberg et al. 1998a & b; Miller et al. 1999; Oberdoester, 2000; Bernstein et al 2001a & b). The importance of durability in differentiating asbestos fiber toxicity between the serpentine mineral fiber chrysotile and the amphibole mineral fibers such as amosite and crocidolite has been addressed more recently (Bernstein & Hoskins, 2006).

DURABILITY:

This leads to the third factor, that of durability. Those fibers whose chemical structure renders them wholly or partially soluble once deposited in the lung are likely to either dissolve completely, or dissolve until they are sufficiently weakened focally to undergo breakage into shorter fibres. The remaining short fibres can then be removed through successful phagocytosis and clearance.

CHEMICAL STRUCTURE AND BIOPERSISTENCE:

The relationship of chemical composition with dissolution and subsequent breakage was first reported by Hammad (1984). Synthetic mineral fibers <5 µm in length had the longest retention in the lung following short-term inhalation, with longer fibers clearing more rapidly and fibers >30 µm in length clearing very rapidly. He proposed that clearance of mineral wools is a result of biological clearance and the elimination of fibers by dissolution and subsequent breakage. However, there was no relationship of these phenomena to long-term toxicological effects.

Early chronic inhalation studies of fibers were often performed without consideration of the respirability of the fibers in the rat and without preserving the length distribution of the fibers. In addition, they were often performed at very high total particle/fiber exposure concentrations. As mineral fibers often occur in bundles of long strands, investigators would grind the fibers to produce a more respirable fraction instead of separating the fibers from the bundles. This process frequently pulverized the rat respirable long fiber fraction producing excessive particles and shorter fibers, sufficient to cause lung overload in the rats.

In 1988, a series of chronic inhalation studies on synthetic mineral fibers (SMF) were performed which took into account the respirability of mineral fibers in the rats and the importance of fiber length in both the preparation of the fibers and the exposure techniques (Hesterberg et al., 1993, 1995; Mast et al., 1995a, 1995b; McConnell et al., 1994, 1995). The results of the studies indicated that the more soluble fibers tested showed little or no pathogenic response, while less soluble fibers showed more response. To further investigate this, a 5 day inhalation protocol was developed for the evaluation of the biopersistence of SMF (Musselman et al., 1994; Bernstein et al., 1994) with numerous fibers analyzed using this protocol (Bernstein et al., 1996; Hesterberg et al., 1998). This 5-day inhalation exposure was proposed by the U.S. Environmental Protection Agency (EPA, 1996) for evaluating the pathological response and biopersistence of inhaled fibers.

The biopersistence protocol was also incorporated by the European Commission (European Chemicals Bureau "Ispra Protocols", EUR 18748 EN, 1999) as part of the European Commission's synthetic fiber directive (European Commission, 1997).

RELATIONSHIP OF BIOPERSISTENCE TO CARCINOGENIC POTENTIAL:

In the series of SVF chronic inhalation studies performed at RCC in the 1980s the relation of the more durable fibers to disease became more apparent and resulted in the design of the inhalation biopersistence study as described above. The importance of fiber length on the potential of a fiber to produce a pathogenic effect was well documented (Lippmann, 1990; McClellan et al., 1992; WHO, 1988; Goodlick & Kane, 1990).

In an analysis that provided the basis for the European Commission’s Directive on synthetic mineral fibers, Bernstein et al. (2001a&b) reported on the correlation between the biopersistence of fibers longer than 20 µm and the pathological effects following either chronic inhalation or chronic intraperitoneal injection studies. As summarized in Table 1, this analysis showed that it was possible using the clearance half-time of the fibers longer than 20 µm as obtained from the inhalation biopersistence studies to predict the number of fibers longer than 20 µm remaining following 24 month chronic inhalation exposure; the early fibrotic response (collagen deposition) observed after 24 months of exposure in the chronic inhalation toxicology studies; and the number of tumours and fiber dose in the chronic intraperitoneal injection studies. These studies, however, only included synthetic mineral fibers.

Table 1 Summary of the correlation between the biopersistence of fibers longer than 20 µm and the pathological effects following either chronic inhalation or chronic intra-peritoneal injection studies. (Bernstein et al., 2001a&b).

THE BIOPERSISTENCE OF FIBERS LONGER THAN 20 µm	CORRELATES WITH:
	<ul style="list-style-type: none"> • The number of fibers L > 20 µm remaining in chronic inhalation toxicology studies following 2 years of exposure. • The early fibrotic response (collagen deposition) observed after 24 months of exposure in the chronic inhalation toxicology studies. • The number of tumours and fiber dose in the chronic intraperitoneal injection studies.

Recent studies on the serpentine asbestos chrysotile have shown that it is not very biopersistent in the lung. As serpentine is a naturally occurring mined fiber, there appears to be some differences in biopersistence depending upon from where it is mined. However, chrysotile lies on the soluble end of this scale and ranges from the least biopersistent fiber to a fiber with biopersistence in the range of glass and stonewools. It remains less biopersistent than ceramic and special purpose glasses and more than an order of magnitude less biopersistent than amphiboles. The 90 day sub chronic inhalation toxicity study of chrysotile in rats shows that an exposure concentration 5,000 times greater than the US-Threshold Limit Value of 0.1 f(WHO)/cm³, chrysotile produces no significant pathological response.

DIFFICULTIES IN INTERPRETING INHALATION TOXICOLOGY STUDIES:

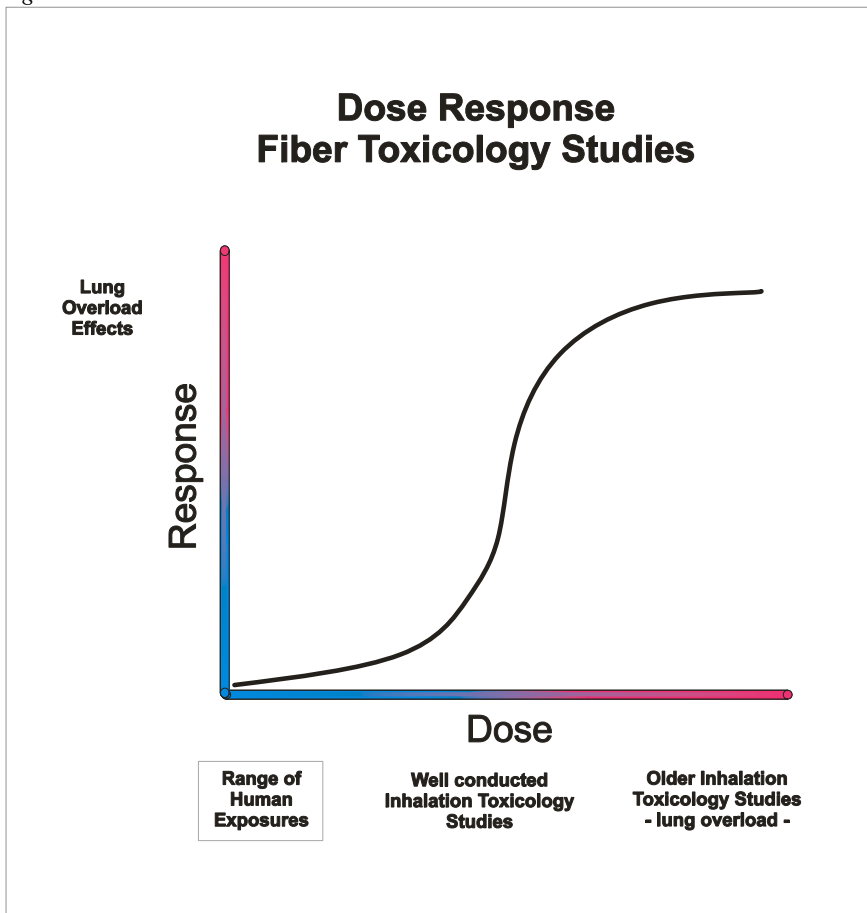
While many chronic inhalation toxicology studies of fibers ranging from amphibole asbestos, to soluble glass fibers and to organic fibers have been performed their design and subsequent interpretation are often confounded by the fiber size distribution and the ratio of longer fibers to

shorter fibers and non-fibrous particles. In many of these studies the exposures often approach and exceed that which has been shown to produce what is now termed 'lung overload' in the rat. Thus, it can become very difficult to compare the effects of such a study with those of another. In most chronic inhalation studies on asbestos, the fiber exposure concentration was determined based upon a gravimetric concentration of 10 mg/m³ without regard for fiber number or size.

High concentrations of insoluble dusts when administered by inhalation in the rat have been shown to overload the lung by compromising the clearance mechanisms, which can result in inflammation and a tumorigenic response (Bolton et al., 1983; Muhle et al., 1988; Morrow, 1988&1992; Oberdorster, 1995a&b).

As illustrated in Figure 4, inhalation toxicology studies are generally performed above the levels at which humans have been exposed. However, when the exposure level is elevated to levels 100,000s times human exposure as occurred in most older fiber inhalation studies with chrysotile and amphibole asbestos, lung overload occurs.

Figure 4



While well-designed chronic inhalation toxicology studies of synthetic mineral fibers have been performed, nearly all chronic inhalation toxicology studies of asbestos have not been designed in a similar fashion. McConnell, et al. (1999) reported on perhaps the only well designed multiple-dose study on any asbestos where amosite particle and fiber number and length chosen to be comparable to the SVF exposure groups. In this hamster inhalation toxicology study the amosite aerosol concentration ranged from 10 to 69 f/cm³ longer than 20 µm and were chosen based upon a previous, multi-dose 90-day subchronic inhalation studies (Hesterberg et al., 1999). No chronic inhalation toxicology studies of chrysotile using similar fibers selection techniques and without exceeding lung over low doses have been performed.

ARE THERE OTHER FIBERS THAT BEHAVE AS CHRYSOTILE?

At acidic pH chrysotile becomes less stable which leads to the clearance/disintegration of the long chrysotile fibers. Kamstrup et al. (2001) described a similar process for long HT fibers which are highly soluble at pH 4.5. The HT fiber has been evaluated in well designed chronic inhalation toxicology study as well as in a chronic intraperitoneal injection study and found to be not carcinogenic. The inhalation biopersistence clearance half-time for this fiber is less than 10 days and has been classified as not carcinogenic by the European Commission and is allowed for use in the United States.

DIFFICULTIES IN INTERPRETING EPIDEMIOLOGY STUDIES:

As fiber related disease in humans takes 30 or more years to develop, the workers evaluated in most asbestos epidemiology studies were exposed from the 1940's to the 1960's. With few exceptions little or no sampling was conducted prior to the 1950s when exposure concentrations were thought generally to be higher than those monitored more recently, due to lack of use of dust control equipment at the time and procedures to reduce dust levels that were introduced only later. For many studies, therefore, early exposures had to be estimated by extrapolation from later measurements.

In a recent analysis of available epidemiological data on the different asbestos types, Berman and Crump (2003) have summarised the various limitations that could influence the epidemiological evaluations and that had to be addressed. These included:

- limitations in air measurements and other data available for characterizing historical exposures;
- limitations in the manner that the character of exposure (i.e., the mineralogical types of fibers and the range and distribution of fiber dimensions) was delineated;
- limitations in the accuracy of mortality determinations or incompleteness in the extent of tracing of cohort members;
- limitations in the adequacy of the match between cohort subjects and the selected control population; and

- inadequate characterization of confounding factors, such as smoking histories for individual workers.

In mixed chrysotile and amphibole asbestos epidemiology studies, the epidemiologists would try to factor the effect of each based upon studies with amphibole alone. However, none of these extrapolations have taken into account the difference in potency of longer amphibole fibers compared to shorter fibers. Thus, if the amphibole study had a larger percentage of longer fibers and the amphibole in the mixed (chrysotile and amphibole) had fewer longer fibers, then the extrapolation would grossly overestimate the contribution from chrysotile.

These factors make it very difficult to assess effects using mixed exposure studies as even a relatively small exposure to long fiber amphibole could account for all the tumorigenic response. It is interesting to note that all epidemiology studies where only exposure was chrysotile have shown no effect.