Asbestos Fiber Types and Dose, and Mesothelioma Risk and Induction

It is well known that there exists a dose-response causal relationship between asbestos exposure and MM, for any fiber type or mixture[39] (Table 43.8).[288] In addition, the amphibole varieties of asbestos are substantially more potent for MM induction than chrysotile[42,288] (Table 43.9),[289] and an extensive review by Hodgson and Darnton[93] on the dose-response relationships between asbestos and mesothelioma risk estimated that the relative potencies for crocidolite, amosite, and chrysotile for mesothelioma induction are roughly 500:100:1, respectively. However, in a subsequent analysis from Australia, based on lung tissue amphibole fiber concentrations allowing for clearance half-lives, Leigh and Robinson[43] calculated the potency ratios to be 26:14:1, respectively, and another set of potency ratios cited in the literature is 30:15:1, respectively.[42]

The factors that determine these differential potencies are sometimes summarized as the three D's: dose, dimensions, and durability (i.e., biopersistence in tissue).[42] Because of their wavy characteristics, chrysotile fibers appear to be trapped more readily within the upper airways and central bronchi than amphibole fibers (Figs. 43.2 and 43.3).[290] In the circumstances of air flow through tubular airways, fibers tend to be concentrated in the central regions of the airway lumen where flow is laminar, with the long axes of fibers parallel to the direction of flow, and fractional deposition of fibers is determined by straight versus curly fiber characteristics and by the diameter of the fibers, rather than their length.[290] Accordingly, Middleton et al.[291] found that the fraction of chrysotile deposited in rats was in the range of 17% to 36% of crocidolite at varying inhaled concentrations, and the deposited fraction of amosite was 65% of crocidolite. Other studies did not detect such differences, but there appears to be general agreement that for exposures in experimental animals lasting for 6 weeks or longer, the relative retention of amphibole fibers is greater than for chrysotile.[290] Fibers and particles most likely to be deposited are those with an aerodynamic equivalent diameter in the range of about 1 to 5 μm, and the sites of greatest deposition are the bifurcations of terminal bronchioles.[290]

TABLE 43.8. Mesothelioma rates in groups exposed occupationally to asbestos, according to fiber types and duration

Fiber type	Industry	Duration (years since first employed)	Rate per 10^6 person-years
Mixed fiber exposure: crocidolite, amosite, and chrysotile	Textile manufacture and insulation	20–24	1520
		25–30	1710
		31+	3180
Mixed fiber exposure: mainly amosite	Insulation workers	20–24	290
		25–29	1550
		30–34	2760
		35–39	6300
		40–44	6330
		45+	8110
Mixed fiber exposure: crocidolite and chrysotile	Fibrous cement manufacture	20–24	2700
		25–29	6300
		30–34	9600
Chrysotile, some crocidolite	Textile manufacture	20–24	108
		25–29	143
		30–34	1156
		35–39	493
		40+	1774
Amosite	Insulation manufacture	20–24	744
		25–29	2623
		30–34	5078
		35+	1842
Mixed fiber exposure	Dockyards	20–24	120
		25–29	410
		30–34	220
		35–40	370
		40–44	1240
		45–49	1510
Crocidolite	Mining and milling	20–24	900
		25–29	2200
		30–34	3000
		35–39	7000

Source: Modified from de Klerk NH, Armstrong BK. The epidemiology of asbestos and mesothelioma. In: Henderson DW, Shilkin KB, Langlois SL, Whitaker D, eds. Malignant mesothelioma, pp. 223–250. Copyright 1992 by Hemisphere. Reproduced with permission of Informa Healthcare Books via Copyright Clearance Center. (See same reference for detailed reference listing.)

TABLE 43.9. Different mineral fibers, their properties, and MM risks

Fiber	MM risk	Aspect ratio[a]	Biopersistence	Human exposure
Erionite (E)	High	High	Persistent	Environmental and residential (Turkey)
Amphibole asbestos				
Crocidolite (C)	High	High	Persistent	Occupational, nonoccupational
Amosite (A)	High but less than C, E	High but less than C	Persistent	Occupational, nonoccupational
Tremolite (T)	Probably high, ?≤C	As for A	Persistent	Environmental, some occupational
Anthophyllite	Low	Fairly low	Persistent	Environmental, formerly restricted occupational (Finland)
Chrysotile	Low, not zero (disputed)	Low	Poor; less than all above	Occupational, nonoccupational
Fiberglass	Zero	Low	Probably poor	Occupational
Ceramic/MMMF	Not documented in humans	High to low	Probably as for amphiboles	Experimental

[a]Length : diameter ratio.
MMMF, man-made mineral fibers.
Source: Modified from Hammar.[289]

Once deposited, amphibole fibers are more persistent in tissues than chrysotile. The clearance half-life in lung tissue has been estimated at 5 to 10 years for crocidolite[292,293] (clearance rate is about 10% to 15% per year) and up to 20 years for amosite fibers,[279] in comparison to 90 to 110 days for chrysotile (although one study[294] recorded a longer clearance half-life of about 8 years for long chrysotile fibers among chrysotile miners/millers in Quebec). Clearance appears to be more effective for short than long fibers—although de Klerk et al.[293] could find no difference between the clearance rates for long and short crocidolite fibers—so that the length of retained fibers increases with time after exposure.[290] Clearance for chrysotile appears to involve both longitudinal and transverse splitting and solubilization of fibers, so that such cleavage can increase the number of fibers per unit weight of lung even after cessation of exposure, before further clearance of fibers accompanied by a diminution in their numbers.[38,295]

To induce MM, deposited asbestos fibers presumably must first translocate to the pleura from the lung where they are deposited initially, but we know of no data on the precise mechanisms and rates at which translocation occurs in humans. However, Boutin et al.[240] demonstrated that asbestos fibers are concentrated in parietal pleural "black spots" located near stomata on the parietal pleura. Amphiboles outnumbered chrysotile in all samples, and 22.5% of fibers in black spots were ≥5 μm in length, which might explain in part why the parietal pleura seems to be the target site for both MM and plaques, and why chrysotile is less potent than the amphiboles (whereas chrysotile appears to be no less potent than the amphiboles when fibers are implanted directly into the pleural cavity of experimental animals). Other studies have demonstrated the presence or even a predominance of chrysotile fibers in human pleural tissue (e.g., see the World Health Organization monograph Environmental Health Criteria 203: Chrysotile Asbestos,[92] pp. 64–65).

Translocation may take place by either migration of naked amphibole fibers, or by ingestion of the fibers by macrophages followed by subsequent transport along lymphatic vessels to the subpleural lymphatic channels.[290] Nonetheless, it seems worth emphasizing that studies on the persistence and clearance of fibers discussed above have focused on lung tissue, obviously not the site where MMs develop, and there appear to be no systematic data for humans on the clearance rates for fibers translocated to the pleura.

The relationship between asbestos inhalation and the subsequent risk of mesothelioma can be expressed by the Peto model and its various modifications[288,296]:

$$I = k \cdot f \cdot (t^p - [t - d]^p)$$

where I is the incidence; k depends on fiber type, mix, size, and other site-specific variables; f is the intensity of exposure in fibers/mL; t is the time in years following exposure; and d is the exposure in years. For the purposes of modeling, variations of the basic equation have been proposed to account for latency period, multiple periods of exposure, weightings for different fiber types in the exposure history, and clearance rates.[297] From the Peto model and its modifications, the following deductions can be inferred:

- Early exposures to asbestos are more significant for MM induction than later exposures, other factors being equal.
- When there are multiple episodes of exposure, each increment of exposure within an acceptable latency interval produces a corresponding increment in the risk/incidence of MM, dependent on the time of the exposure, its magnitude, and the types of asbestos fiber involved. This issue was discussed at some length in the World Trade Organization (WTO) report on asbestos (specifically chrysotile),[42] and the dose-response relationship between asbestos and mesothelioma was illus-

trated in tabular form by de Klerk and Armstrong in 1992[288] (Table 43.8).

Is a Threshold or Minimal Level of Asbestos Exposure/Inhalation Required for Mesothelioma Induction?

No minimum threshold dose of inhaled asbestos has been delineated below which there is no increase in the risk of mesothelioma.[92,93,176,189,212,217] In a study on time trends and occupational risk factors for pleural mesothelioma in Sweden, based on the Swedish Family-Cancer Database, Hemminki and Li[212] found an increasing age-adjusted incidence of pleural mesothelioma over the period 1961–1998, not only for occupations expected to be associated with asbestos exposure (manual and blue-collar workers), but also in professional groups and even farmers.

In relation to the no-threshold model for mesothelioma induction by asbestos, reviews and several case-control studies from Europe are of particular relevance and include the following:

- A review by Hillerdal[163] on mesothelioma related to nonoccupational asbestos exposure was published in 1999. It is of particular interest in relation to mesotheliomas as a consequence of low-level exposures to asbestos.
- A review and meta-analysis by Bourdès et al.[298] of the risk of pleural mesothelioma from environmental exposure to asbestos was published in 2000. These authors identified eight relevant studies on the risk of pleural mesothelioma from household or neighborhood exposures to asbestos. These studies did not include the case-control studies outlined below. These authors found that the RRs of pleural mesothelioma for household exposure ranged between 4.0 and 23.7, with a summary risk estimate of 8.1 (95% CI, 5.3–12). For neighborhood exposures, the RRs ranged between 5.1 and 9.3 with a summary estimate of 7.0 (95% CI, 4.7–11). This analysis appears to be in reasonable agreement with the studies by Magnani et al.[299,300] and Rödelsperger et al.[301] (see below). Bourdès et al.[298] commented that their data were insufficient to estimate the magnitude of excess risk at the levels of environmental exposure commonly experienced by the general population in industrial countries (in other words, from the general environment).
- In a case-referent study reported from France by Iwatsubo et al.,[91] it was found that the odds ratio for mesothelioma (OR_{MM}) was 4.2 with low-dose exposures in the range of 0.5 to 0.99 fibers/mL-years (fiber-years). In this study, there was a clear dose-response trend from no exposure, through levels of 0.001 to 0.49 fiber-years, 0.5 to 0.99 fiber-years, 1.0 to 9.9 fiber-years, and >10 fiber-years with age and socioeconomic, class-adjusted ORs (RRs) of 1.0 (for no exposure), 1.2, 4.2, 5.2, and 6.7, respectively. Although the OR_{MM} of 1.2 at 0.001 to 0.49 fiber-years did not achieve statistical significance, further calculations show a highly significant trend. Furthermore, it has been suggested that this study lacked statistical power because the number of subjects was too small to detect an $OR_{MM} = 1.2$ at the usual scientific level of significance. Accordingly, this study[91] is not inconsistent with a no-threshold model.
- In a case-referent study reported from Germany by Rödelsperger et al.,[301] the OR_{MM} was >4.5 with lung tissue asbestos fiber concentrations in the range of 100,000 to 200,000 fibers longer than 5 μm per gram of dry lung tissue, and an OR_{MM} of about 2 or more was recorded for lower lung tissue asbestos fiber concentrations, in the range of 50,000 to 100,000 fibers longer than 5 μm per gram dry lung.
- In a meticulous case-referent analysis published in 2001 using individualized estimates of exposures, Rödelsperger et al.[94] found that the OR_{MM} was 7.9 with low exposures in the range of anything more than 0 to 0.15 fibers/mL-years (>0–0.15 fiber-years). Similar findings were reported by Magnani et al.[299]
- In a population-based study on the distribution of mesothelioma in California, after attempted allowance for occupational exposures, Pan et al.[302] reported an apparent direct correlation between the odds of mesothelioma and proximity of residence according to the distribution of ultramafic rocks in the general environment (serpentinite/ultramafic rocks in California contain mainly chrysotile, with some other forms of asbestos in some areas, such as tremolite). These authors found about a 6% reduction in the odds of mesothelioma for residence for every 10 km further away from the ultramafic rocks.
- As set forth in their review on dose-response relationships between asbestos and mesothelioma, Hodgson and Darnton[93] estimated that a cumulative exposure of 1.0 fiber/mL-year for crocidolite yields a lifetime risk "best" estimate of about 650 mesothelioma deaths/100,000 (range = 250–1500), 90/100,000 for amosite (range = 15–300), and 5/100,000 for chrysotile (range = 1–20). For a cumulative exposure of 0.1 fibers/mL-years, these authors set forth a best estimate of about 100 deaths per 100,000 exposed for crocidolite, with a highest arguable estimate of 350 and a lowest of 25; for amosite, the corresponding figures were 15 deaths per 100,000, with a highest arguable estimate of 80 and lowest of 2; at this level of exposure, the risk for chrysotile was "probably insignificant," with a highest arguable estimate of four deaths per 100,000. For a cumulative exposure of 0.01 fibers/mL-years, the best estimate was about 20 deaths per 100,000 exposed for crocidolite, with a highest arguable estimate of 100 and a lowest of two; for amosite, the corresponding figures