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REVIEW ARTICLE

Asbestos fiber length and its relation to disease risk

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ABSTRACT

Differences in chemical and crystalline composition, fiber dimension, aerodynamic characteristics and biodurability are among the critical factors that define the toxicological and pathological consequences of asbestos exposure. Specifically, fiber dimension can impact whether the fiber is respired, whether and how deeply it is deposited in the lung, and how efficiently and rapidly it may be cleared. This paper provides a current, comprehensive evaluation of the weight of evidence regarding the relationship between asbestos fiber length and disease potency (for malignant and nonmalignant endpoints). *In vitro* studies, animal exposure studies and epidemiology data were reviewed. We found that the data reported over the last several decades consistently support the conclusions that exposure to fibers longer than 10 μm and perhaps 20 μm are required to significantly increase the risk of developing asbestos-related disease in humans and that there is very little, if any, risk associated with exposure to fibers shorter than 5 μm. Fiber length as a predictor of potency has been evaluated by several federal agencies in the U.S. and could significantly influence future regulatory decisions for elongated mineral particles (EMPs) and high-aspect ratio nanoparticles (HARNs).

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Introduction

Asbestos has been utilized extensively since ancient times because of a number of unique and valuable qualities, including the high tensile strength and superior insulating ability of this class of minerals. In addition to these desirable physical and chemical characteristics, several different asbestos minerals were readily available, inexpensive and easy to process into end-products. Consequently, the commercial applications of asbestos expanded dramatically during the first half of the twentieth century.

A significant amount of research has been devoted to understanding the characteristics of asbestos fibers that are responsible for their disease-inducing potential. It has been recognized for some time that not all asbestos fibers are the same and that differences in chemical and crystalline composition, fiber dimension, aerodynamic characteristics, and biodurability are among the critical factors that influence the potential toxicity of an asbestos fiber. King et al. (1946) were the first to document in the published literature fiber length differences in the fibrogenic potential of asbestos. Subsequent studies showed that the presence of longer, thinner fibers regardless of the type of asbestos was more likely to result in fibrosis and tumorigenesis than short fibers (Berman et al., 1995; Ilgren & Chatfield, 1998a,b; Lippmann, 1988, 1994; Miller et al., 1999; Stanton, 1973; Stanton et al., 1977, 1981; Vorwald et al., 1951).

It is only relatively recently, however, that weight of evidence analyses have suggested that a threshold fiber length may exist for many, if not all, asbestos fiber types; the risk of disease would not be significantly increased even at very high exposures below this fiber length. In 2002, the Agency for Toxic Substances and Disease Registry (ATSDR) convened a panel to discuss the degree to which fiber length influences the onset of asbestos-related cancer (ATSDR, 2002). After reviewing various epidemiological, animal, and *in vitro* studies, the ATSDR-sponsored panel concluded that "asbestos … shorter than 5 μm are unlikely to cause cancer in humans" (ERG, 2003a, p. vi). Similarly, a 2003 U.S. Environmental Protection Agency (EPA) report commissioned to examine this issue concluded that, based on mathematical modeling, "the optimum cutoff for increased potency occurs at a length that is closer to 20 μm than 10 μm" (Berman & Crump, 2003, p. 7.61). An EPA-sponsored expert panel convened to evaluate and comment on the technical support document and agreed that the cancer "risk for fibers less than 5 μm in length is very low and could be zero" (ERG, 2003b, p. viii). Some researchers continue to maintain that, because short fibers (<5 μm) often predominate (relative to longer fibers) in human lung tissue samples, they must be associated with some degree, and possibly a substantial degree, of cancer risk (Dodson et al., 2003; Suzuki & Yuen, 2001; Suzuki et al., 2005).

The purpose of this paper is to provide a current state of the science review regarding asbestos fiber length and disease potential. Malignant (lung cancer and pleural mesothelioma) and nonmalignant (fibrosis) endpoints are evaluated. The current weight of evidence regarding *in vitro* studies, animal studies and asbestos-exposed worker cohorts is summarized and interpreted. This analysis is timely because numerous relevant studies, particularly epidemiology

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studies of worker cohorts exposed primarily to short fiber asbestos, have been published since the EPA and ATSDR panels convened approximately 15 years ago. In addition, it appears that fiber length as a predictor of disease potential could significantly influence future regulatory decisions for elongated mineral particles (EMPs) and high-aspect ratio nanoparticles (HARNs).

Methods

A comprehensive literature review was conducted of all publically available documents that expressly examined the effect of fiber length on the development of asbestos-related disease, specifically asbestosis, lung cancer and mesothelioma. Several database search engines (e.g. PubMed and ToxNet) were used to identify relevant reports, literature or conference proceedings. The search was not restricted based on asbestos fiber type, animal model or fiber delivery method. Due to inter-laboratory variation, the discussion of studies was limited to those that directly compared short versus long asbestos fiber preparations. Although the focus of this review is on fiber length in relation to asbestos exposure, when appropriate, studies relating to EMP and HARN exposure are discussed.

Fiber length and asbestos toxicity

Since humans can differ quite significantly from animals in their reaction to toxic agents, most scientists prefer to base risk estimates for humans on human data. This is because in order to apply animal or tissue culture data to humans, scientists must extrapolate from one species to another or from simple cellular systems to the complexities of human physiology. In terms of the respiratory system, the complexities that dictate how a chemical or particle is absorbed or deposited in the lungs and interacts with specific cells is dependent on a multitude of different factors, including the (1) physical and chemical nature of the agent, (2) respiration patterns and lung function of the individual, (3) anatomy, cellular population and metabolic makeup within different regions of the lung and (4) intra- and extra-pulmonary cellular and chemical signaling. These interactions are virtually impossible to replicate *in vitro*. However, in some circumstances, where human data are limited, laboratory studies including those on animals may provide the only basis from which risk can be estimated; as such, numerous *in vitro* and *in vivo* studies have been conducted to investigate asbestos toxicity in relation to fiber length.

Fiber length and human studies

Few, if any, human asbestos cohorts are known in which individuals were exposed only to short fibers in high exposure scenarios (i.e. work with raw fiber). While mining and milling involved exposure to raw fibers that encompassed a very wide range of fiber lengths, the cement, friction and textile manufacturing industries relied on processed fibers of a relatively specific length distribution. Cement and friction manufacturing industries primarily used short and medium length chrysotile fibers (Grades 4–7), while the textile industries required the use of much longer fibers (Grades 1–3) (Cossette & Delvaux, 1979; Mann, 1983; Pigg, 1994). Grades 1 and 2 consist of unprocessed or crude chrysotile asbestos, while Grades 3 through 7 are milled chrysotile of decreasing fiber lengths that are produced by mechanical techniques such as crushing, screening and air separation.

Some researchers have suggested that occupational studies usually provide little insight into questions of fiber length and risk because workers were often exposed to a wide range of fiber sizes (Doll & Peto, 1985; Meldrum, 1996). While this may generally be true, it has been noted that the differences in lung cancer risk associated with the chrysotile textile industry and chrysotile mining and milling may be the result of differences in fiber size distributions (Huncharek, 1987; Meldrum, 1996). For example, in 1983, McDonald et al. (1983a) performed a follow-up evaluation on the South Carolina textile worker cohort previously evaluated by Dement et al. (1982) and observed a steep linear exposure–response (mortality) that was approximately 50-fold greater than in Canadian chrysotile mining and milling cohorts. In a separate investigation, McDonald et al. (1983b) investigated potential differences between mining and manufacturing with chrysotile and amphiboles among a group of Pennsylvania textile workers with opportunities for exposure to chrysotile, amosite and crocidolite. The authors reported that the risk of lung cancer in textile processing was much greater than in production. Hughes & Weill (1986) suggested that the state and physical treatment of asbestos in different industries created dust clouds with asbestos fibers of differing physical dimensions, thereby resulting in differences in carcinogenic potential. They specifically noted that textile manufacturing facilities are likely to offer opportunities for exposure to long, thin fibers relative to those experienced in mining and milling settings. Similarly, Nicholson (1991, 2001), Nicholson & Landrigan (1994, 1996) and Nicholson & Raffn (1995) hypothesized that the percentage of thin, uncounted, but highly carcinogenic fibers at textile plants may be greater than in the mining and milling environments, thereby allowing for a greater observed cancer risk at the same measured cumulative fiber exposure.

In 1994, Dement et al. provided an update of the South Carolina textile worker cohort originally discussed in their 1981 and 1983 publications (Dement et al., 1994). The authors supported the conclusion that the difference in fiber size distributions was the cause for differences in lung cancer risk between chrysotile-exposed textile workers and chrysotile miners. Dement et al. (2008, 2009) later derived fiber size specific exposure estimates for multiple exposure zones at the North Carolina and South Carolina textile manufacturing facilities. They concluded that the "vast majority" of fibers inhaled by textile workers were shorter than 5 µm in length (Dement et al., 2008, p. 583; Dement et al., 2009, p. 611). Although some have suggested that the presence of more short fibers means they are more potent, work from Dement et al. suggest that lung cancer risk increased with increasing fiber length. Using the previously published exposure estimates stratified by fiber size, Loomis et al. (2012) analyzed

whether the risk of lung cancer varies with fiber length and diameter in these cohorts and concluded that the occurrence of lung cancer is associated most strongly with exposure to long, thin asbestos fibers. It should be noted that the authors only adjusted for age, sex, race and calendar year; smoking status was not considered.

More recently, Pierce et al. (2016) examined chrysotile asbestos no-observed adverse effect levels (NOAELs) for lung cancer and mesothelioma. Like earlier studies, the authors determined that there is likely an important role for fiber length with respect to disease risk. They noted that occupational cohorts of industries that historically used shorter chrysotile fibers, including friction and cement product manufacturing, did not demonstrate an increased risk of either mesothelioma or lung cancer. Specifically, the authors reported that no friction or cement product manufacturing cohorts included in their analysis reported an increased disease risk at any exposure level. The absence of disease in the short fiber manufacturing cohorts, such as friction and cement manufacturing, is consistent with numerous epidemiology studies that reported no increased risk in workers who handled the manufactured chrysotile products (Garabrant et al., 2016; Laden et al., 2004). Conversely, all of the studies of textile cohorts reported an increased risk of disease at one or more exposure level. As pointed out by Pierce et al. (2016), the degree to which any present short fibers contributed to disease onset in the textile cohorts is not clear due to the potential masking effect of the long fibers. Similarly, Berman and Crump have indicated that although exposure to longer fibers among textile cohorts demonstrably increases the risk of asbestos-related disease, the data "do not necessarily mean that shorter fibers are nonpotent" (Berman & Crump, 2008a, p. 65).

Animal studies examining disease outcomes

Asbestos can be delivered experimentally via multiple routes, including inhalation, intratracheal instillation, or intrapleural and intraperitoneal injection. Inhalation studies have more convincingly demonstrated the importance of fiber length in mesothelioma, lung cancer and pulmonary fibrosis. There are distinct differences in the distribution, clearance and retention of materials when administered by instillation compared to inhalation. Inhalation provides a natural route of entry into the lungs, whereas instillation is a nonphysiologic and invasive route of entry. Although the actual dose delivered to the lungs of each animal can be essentially assured with injection/instillation, the distribution of material within the respiratory tract differs since the upper respiratory tract is bypassed (Brain et al., 1976; Driscoll, 2000; Mossman et al., 2011). As such, the emphasis for the discussion below is on animal inhalation studies.

Fibrosis

The importance of fiber length in pulmonary fibrosis has been shown in studies using asbestos. Table 1 summarizes asbestos fiber type, length, exposure parameters and fibrotic outcome after exposure to asbestos in multiple animal studies. Following the review of experimental studies in animals after injection or inhalation of asbestos fibers, Lippmann (1988) concluded that asbestosis most closely related to the surface area of retained fibers. To date, there have been several animal inhalation studies that have examined the influence of the fiber length on the pathology of asbestos.

In 1951, Vorwald et al. reported the results of extensive investigations performed by Gardner at the Saranac Laboratory over the course of the previous twenty years (Vorwald et al., 1951). As part of this effort, Gardner evaluated several types of asbestos at a range of fiber lengths in multiple animal species by a variety of exposure routes. In the inhalation experiments, guinea pigs, rabbits, cats, rats and/or mice were exposed to either asbestos dust collected during the carding operation at a fabrication plant (~1% >10 μm), ball-milled chrysotile (0.6% >10 μm), or chrysotile asbestos up to 50 μm in length (6.7% >10 μm). Guinea pigs exposed to ball-milled chrysotile for 28 months demonstrated slight peribronchiolar fibrosis, whereas those exposed to long chrysotile reported definitive fibrosis at 16 months. Fibrosis developed in both rats and mice exposed to long chrysotile, but not ball-milled chrysotile. In a companion evaluation, this group compared short and long fiber dusts by intratracheal injection. While no fibrosis was observed with short fiber chrysotile, amosite, crocidolite or tremolite, distinct fibrosis was observed with long fiber preparations of these same fiber types. Evidence of fibrosis was not observed with either short or long fiber anthophyllite. Based on his extensive research, Vorwald et al. concluded that peribronchiolar fibrosis is produced by asbestos fibers between 20 and 50 μm in length, but not by fibers shorter than 20 μm.

Crapo et al. (1980) administered short and intermediate-length National Institute of Environmental Health and Sciences (NIEHS) chrysotile to rats by inhalation. After three months, both fiber preparations caused similar increases in the volume of alveolar epithelium, interstitium and alveolar macrophages. However, after 12 months, greater lung injury was observed in animals treated with the intermediate fiber preparation. In a similar experiment published in 1980, Wagner et al. exposed rats via inhalation to SFA (super fine sample), grade 7, and UICC (Union Internationale Contre Le Cancer) Canadian chrysotile and reported a similar progression of early fibrosis for all three chrysotiles (Wagner et al., 1980). Although the specific distribution was not reported, the authors reported that SFA fibers were longer than grade 7 fibers, which were longer than the UICC fibers. In 1990, Wagner reported differences in the pleural reaction in rats after inhalation to unreported concentrations of crocidolite and disc-milled crocidolite (Wagner, 1990). Those animals exposed to UICC crocidolite began showing signs of fibrosis after 12 months, whereas those exposed to the shortened crocidolite only showed an early interstitial reaction.

Davis et al. (1986b) exposed rats to short and long amosite by inhalation. While there was no evidence of fibrosis in animals exposed to short fiber amosite, rats exposed to long fiber amosite showed progressive thickening of the alveolar septa and accumulation of fibrous tissue. Fibrosis was

Table 1. Animal studies examining fibrosis in relation to fiber length after exposure to asbestos.

Type of asbestos	Animal model	Exposure concentration	Exposure duration	Particle length	Summary	Study
Mode of delivery: inhalation						
CH	Cat; Gpg; Mus; Rat	32–150 mppcf	8 h/d, up to 54 months	Short: ~1% >10 μm Milled: 0.6% >10 μm Long: 6.7% >10 μm	Peribronchiolar fibrosis is produced by asbestos fibers between 20 μm and 50 μm in length, but not by particles shorter than 20 μm.	(Vorwald et al., 1951)
CH	Rat	10.8 mg/m^3	7.5 h/d, 5 d/week, up to 2 years	UICC: 3750 f/cc >5 μm Grade 7: 1020 f/cc >5 μm SFA: 430 f/cc >5 μm	The UICC chrysotile resulted in at least as much fibrosis as the other two chrysotiles.	(Wagner et al., 1980)
CH	Rat	3.1–9.4 mg/m^3	7 h/d, 5/week, up to 12 months	Short: >90% <5 μm Intermediate: significant no. >20 μm	After three months, both fiber preparations caused similar increases in the volume of alveolar epithelium, interstitium and alveolar macrophages. However, after 12 months, greater lung injury was observed in animals treated with the intermediate fiber preparation.	(Crapo et al., 1980)
AM	Rat	11.6–11.9 mg/m^3	7 h/d, 5 d/week, 224 days	Short: 1% >5 μm Long : 30% >5 μm	Observed no fibrosis in short AM exposed animals at any stage, but progressive interstitial fibrosis in the long AM group.	(Davis et al., 1986b)
CH	Rat	10 mg/m^3	5 d/week, 12 months	Short: 1170 fibers >5 μm Long: 5510 fibers >5 μm	Animals treated with long fiber samples developed six times more advanced interstitial fibrosis than animals treated with short fiber samples. Signs of fibrosis were visible at 12 months.	(Davis & Jones, 1988)
CH	Rat	7.78–11.36 mg/m^3	7 h/d, 5 d/week, 12 months	Coalinga: short UICC/B: long Jeffrey: long	The two long chrysotiles were fibrogenic at 12 months, while Coalinga chrysotile was not fibrogenic twelve or 24 months following exposure.	(Ilgren, 2002; Ilgren & Chatfield, 1997, 1998a)
CR	Mky	212 f/cc	Not specified	Fine: <5 μm UICC, coarse: 5–100 μm	Lesions were observed in the monkeys exposed to coarse crocidolite, while the response to fine crocidolite produced only a slight response consisting primarily of dust-containing alveolar macrophages in the perivascular tissue.	(Webster, 1970)
CR	Rat	NR	7 h/d, 5 d/week, up to 24 months	UICC, milled UICC, unmilled: 52.6% >5 μm	Animals exposed to long fibers had minimal fibrosis while short fibers only induced a tissue reaction.	(Wagner, 1990)
Mode of delivery: intratracheal						
AM	Gpg	50 mg	2 injections; 2 weeks apart	Short: ≤20 μm Long: 20–50 μm	Long fiber showed typical fibrous endobronchiolitis and peribronchiolitis. The short fiber reaction was limited to phagocytosis with lymphocytic infiltration of adjacent walls.	(Vorwald et al., 1951)
AM	Rat	1 mg/0.1 mL	10 total injections; weekly	Short: $\chi = 3.8$ μm Long: $\chi = 16.6$ μm	Long amosite fibers significantly decreased the number of alveolar macrophages, increased the number of granulocytes, and depressed phagocytic activity and the viability of alveolar macrophages, while short amosite fibers only decreased the number of alveolar macrophages and increased their phagocytic activity.	(Hurbankova & Kaiglova, 1997)
AN	Gpg	50 mg	2 injections; 2 weeks apart	Short: ≤3 μm Long: 20–50 μm	No fibrosis from short fiber or long fiber preparations.	(Vorwald et al., 1951)
CH	Gpg	50 mg	2 injections; 2 weeks apart	Short: ≤3 μm Long: 20–50 μm	Fibrosis only seen with long fiber preparations.	(Vorwald et al., 1951)
CH	Gpg	3–25 mg	2–6 injections	Short: 1.6% ≥10 μm Long: 23.6% ≥10 μm	Longer fiber preparations produced marked fibrosis, whereas short fiber samples caused only a macrophage reaction.	(Kuschner & Wright, 1976)
CH	Rat	10 mg	Single dose	Short: $\chi = 2.5$ μm Long: $\chi = 15$ μm	Moderate peribronchiolar fibrosis was observed in only 15% of short-fiber treated rats, while marked interstitial fibrosis was reported in 64% of the longer-fiber group.	(Smith et al., 1951)
CH	Rat	25–50 mg	Single dose	A: $\chi = 2.5$ μm B: $\chi = 17.6$ μm	Chrysotile B fibers created a nodular, compact fibrosis, while chrysotile A showed normal lungs even after 180 days.	(Burger & Engelbrecht, 1970a)

(*continued*)

Table 1. Continued

Type of asbestos	Animal model	Exposure concentration	Exposure duration	Particle length	Summary	Study
CH	Rat	5 mg	Single dose	Short 4T30: 98% <3 μm UICC B: 42% >5 μm	While UICC chrysotile caused severe fibrosis around the terminal bronchioles, short 4T30 chrysotile did not induce fibrotic lesions.	(Lemaire et al., 1985)
CH	Rbt	100 mg	Monthly	Short: $\chi = 2.5$ μm Long: $\chi = 15$ μm	Interstitial fibrosis was observed at both fiber lengths, although a more diffuse response was observed with the shorter fibers.	(King et al., 1946)
CR	Gpg	50 mg	2 injections; 2 weeks apart	Short: ≤20 μm Long: 20–50 μm	Long fiber preparations induced fibrous endobronchiolitis and peribronchiolitis, while short fiber preparations showed signs of peribronchiolitis, but no fibrosis.	(Vorwald et al., 1951)
CR	Gpg	3–25 mg	2–8 injections	Short: 99% <5 μm Long: 80% >10 μm	Longer fiber preparations produced extensive interstitial fibrosis, whereas short fiber samples caused only a macrophage reaction.	(Wright & Kuschner, 1975)
CR	Gpg	3–25 mg	2–8 injections	Short: 2% ≥10 μm Long: 82.2% ≥10 μm	Longer fiber preparations produced marked fibrosis, whereas short fiber samples caused only a macrophage reaction.	(Kuschner & Wright, 1976)
CR	Mus	0.1 or 0.5 mg	Single dose	Short: $\chi = 0.6$ μm ± 0.1 Long: $\chi = 24.4$ μm ± 0.5	Long fibers induced fibrous tissue while the short fibers were regularly phagocytized and appear to not induce fibrosis.	(Adamson & Bowden, 1987a,b)
CR	Mus	0.1 mg	Single dose	Short: $\chi = 0.6$ μm ± 0.1 Long: $\chi = 24.4$ μm ± 0.5	While short fibers induced only a small increase in labeling of bronchiolar epithelial and interstitial cells, long fibers damaged bronchiolar epithelium and became incorporated into connective tissue as well as inducing fibrosis.	(Adamson et al., 1993)
TR	Gpg	50 mg	2 injections; 2 weeks apart	Short: ≤20 μm Long: 20–50 μm	While long fiber preparations resulted in fibrosis, short fiber preparations resulted only in a simple foreign body reaction.	(Vorwald et al., 1951)
Mode of delivery: intrapleural						
AM	Mus	5 μg	Single dose	Short: 4.46% >15 μm Long: 50.36% >15 μm	Long fiber preparations produced inflammation and granuloma reactions leading to progressive fibrosis, whereas short fiber preparations did not.	(Murphy et al., 2011)
CH	Mus	10 mg	Single dose	Short Normal	'Normal' fiber preparations produced widespread cellular granulomata gradually replaced by fibrous tissue, while short fiber preparations produced much smaller granulomata and no adhesions.	(Davis, 1972)
CH; CR	Rat	50 mg	Single dose	CH Short: $\chi = 2.52$ μm CH Long: $\chi = 16.18$ μm CR Short: $\chi = 3.43$ μm CR Long: $\chi = 11.45$ μm	After 120 days, the reaction produced by crocidolite was not substantially different from that observed with chrysotile. However, pleural fibrosis was more pronounced with the long-fibered asbestos preparations than with the short-fiber preparations.	(Burger & Englebrecht, 1970b)
Mode of delivery: intraperitoneal						
AM	Mus	5–2500 μg	Single dose	Short: 0.1–0.2% >10 μm Long: 10–12% >10 μm	Macrophage and neutrophil recruitment in the peritoneal cavities was more pronounced in the long fiber group.	(Donaldson et al., 1989)
AN	Gpg	0.2 g	Single dose	Ball-milled: <3 μm Long: ≤100 μm	Short fiber preparations resulted in an "essentially" inert foreign body reaction, whereas long fiber preparations produced distinct early fibrosis.	(Vorwald et al., 1951)
CH	Gpg	0.2 g	Single dose	Ball-milled: <3 μm Long: through 100 mesh	Long fiber preparations produced definite fibrosis, where ball-milled preparations did not produce fibrosis or asbestos bodies.	(Vorwald et al., 1951)
CH	Rat	25 mg	4 injections	Milled: 99.8% <5 μm Unmilled: 93.9% <5 μm	Milling reduced the severity of the resultant fibrosis.	(Pott et al., 1972, 1974)

AM: amosite; AN: anthophyllite; CH: chrysotile; CR: crocidolite; TR: tremolite; Mus: mouse; Gpg: guinea pig; Mky: monkey; Rbt: rabbit.

observed in 11% of the long fiber group. In 1988, Davis and Jones administered short and long UICC chrysotile by inhalation to rats (Davis & Jones, 1988). Fibrosis was observed in 12.6% of animals treated with long fiber chrysotile and in 2.4% of animals in the short fiber group.

The potential fibrogenicity of Coalinga, UICC/B and Jeffrey chrysotile was assessed in two inhalation animal studies; the first conducted by the NIEHS in 1978 and the other at the Fraunhofer Institute in 1983. Ilgren (2002) and Ilgren and Chatfield (1997) reexamined histopathological slides from the above mentioned animal inhalation studies and reported that the long fiber preparations (UICC/B and Jeffrey) were fibrogenic at 12 months, while the short fiber preparation (Coalinga) was not fibrogenic.

Asbestos related cancer: lung cancer and pleural mesothelioma

Classical studies by the Stanton and Pott laboratories have indicated that the induction of mesothelioma by any asbestos fiber is directly related to the presence of fibers >8 µm in length and <0.25 µm in diameter (Pott, 1978; Pott et al., 1972; Stanton & Wrench, 1972; Stanton et al., 1977, 1981). Although some studies have suggested that short fiber asbestos preparations may be carcinogenic after injection, these preparations also contained a small percentage of long fibers, making results difficult to interpret. Moreover, it is apparent from a dose response study by Davis & Jones (1988) that short fiber preparations elicit a response at higher "overload" doses, but not at lower doses (Oberdorster, 1995). Table 2 summarizes asbestos fiber type, length, exposure parameters and disease outcome after exposure to asbestos in multiple rodent studies.

In addition to describing the occurrence of asbestos-induced fibrosis, Vorwald et al. (1951) did not observe evidence of lung cancer or mesothelioma among the control or treated animals following administration of varying lengths of asbestos by inhalation, intrapleural, intratracheal or intravenous administration. Beginning in the early 1970s, a series of animal inhalation studies were conducted indicating that relatively short fibers (≤8 µm) are more easily inactivated by cellular phagocytosis than longer fibers and thus are less capable of inducing asbestos-related diseases, including mesothelioma (Stanton, 1973; Stanton et al., 1977, 1981). In 1988, Lippmann reported that mesothelioma induction is most closely associated with the number of fibers longer than ~5 µm and thinner than ~0.1 µm, whereas lung cancer is most closely associated with fibers longer than ~10 µm and thicker than ~0.15 µm (Lippmann, 1988). Following an analysis of fiber length distribution data from rat inhalation studies using amosite, brucite, chrysotile, crocidolite, erionite and tremolite as test materials in 1994, Lippmann also concluded that the concentration of fibers longer than either 10 or 20 µm in length is a better predictor of tumor yield than is the concentration of fibers longer than 5 µm (Lippmann, 1994).

Berman et al. (1995) and Berman & Crump (2003) evaluated data from 13 rat inhalation bioassays in which the animals were exposed to nine different types of asbestos dusts, including UICC crocidolite, Korean tremolite, four types of chrysotile, and three types of amosite. Berman et al. relied on a series of animal inhalation studies conducted by Davis et al. (1986a, 1985, 1986b, 1978, 1980) and Davis & Jones (1988). In these studies, male AF/HAN rats were exposed to 2–10 mg/m^3 asbestos by inhalation for seven hours per day, five days per week for 224 days to over one year. Berman et al. concluded that structures contributing to lung tumor risk appeared to be long (≥5 µm) and thin (0.4 µm) fibers and further noted that potency appeared to increase with increasing length, with structures longer than 40 µm being approximately 500 times more potent than those between 5 and 40 µm in length. These researchers suggested that structures less than 5 µm in length did not contribute to lung tumor risk.

In the above-mentioned reanalysis of the NIEHS animal inhalation study with Coalinga, UICC/B and Jeffrey chrysotile, Ilgren & Chatfield (1998a) reported that the incidence of pulmonary tumors in Coalinga exposed animals was the same as the untreated control animals. In contrast, greater than 20% of the animals exposed to both Jeffrey and UICC/B chrysotile exhibited pulmonary tumors. There were no mesotheliomas in these exposure groups. Perhaps most importantly, Wagner (1990) reported no cases of mesothelioma among the animals exposed by inhalation to shortened erionite and almost a 100% incidence of mesothelioma among the 27 animals exposed to longer-fiber erionite. This finding is of particular interest because long erionite fibers are thought to be one of the most, if not the most, potent inducers of mesothelioma.

Contrary to the other inhalation studies with short asbestos fibers, Wagner et al. (1980) reported that approximately 16, 11 and 25% of the animals exposed to SFA, grade 7 and UICC chrysotile, respectively, developed lung tumors. There was one reported mesothelioma in an SFA chrysotile exposure animal. The airborne fiber concentrations [reported as fibers longer than 5 µm by phase contrast microscopy (PCM)] measured in the exposure chamber "dust clouds" during this study was 430, 1020 and 3750 f/cc, respectively. The concentrations measured were well above fiber concentrations measured in even the dustiest asbestos industries and likely overloaded the lung by compromising the clearance mechanisms.

Summary

In general, results are difficult to evaluate because of different experimental protocols (e.g. differing concentrations, mode of delivery, and species). However, data from a number of experiments overwhelmingly support the concept that the risks of lung cancer, mesothelioma, and fibrosis increase with increasing fiber length. Short fibers in these studies have shown much less fibrogenic and carcinogenic activity than long fibers, regardless of the potency of longer fibers of the same fiber type. Moreover, chronic inhalation of very high doses of short chrysotile fibers (≤5 µm in length) for lifetime exposures (2 years) in rats or 28 months in baboons yielded no fibrosis or pulmonary tumors despite the

Table 2. Animal studies examining asbestos-related cancer in relation to fiber length after exposure to asbestos.

Type of asbestos	Animal model	Exposure concentration	Exposure duration	Particle length	Control animals	Animals with pulmonary tumors: Short	Animals with pulmonary tumors: Long	Study
Mode of delivery: inhalation								
AM	Rat	11.6–11.9 mg/m^3	7 h/d, 5 d/week, 224 days	Short: 1% >5 μm Long : 30% >5 μm	Group 1: 2/36 (0 MM) Group 2: 0/25	1/42 (1 MM)	14/40 (3 MM)	(Davis et al., 1986b)
CH	Rat	10.8 mg/m^3	7.5 h/day, 5 d/week between 6 months and 2 years	UICC: 3750 f/cc >5 μm Grade 7: 1020 f/cc >5 μm SFA: 430 f/cc >5 μm	1/71 (0 MM)	SFA: 13/80 (1 MM) Grade 7: 9/81 (0 MM)	UICC: 20/81 (0 MM)	(Wagner et al., 1980)
CH	Rat	10 mg/m^3	5 d/week, 12 months	Short: 1170 fib >5 μm Long: 5510 fib >5 μm	2/47 (0 MM)	8/40 (1 MM)	23/40 (3 MM)	(Davis & Jones, 1988)
CH	Rat	7.78–11.36 mg/m^3	7 h/d, 5 d/week, 12 months	Coalinga: short UICC/B: long Jeffrey: long	2/53 (0 MM)	2/51 (0 MM)	UICC B: 13/54 (0 MM) Jeffery: 10/51 (0 MM)	(Ilgren & Chatfield, 1997, 1998a)
CR	Rat	10 mg/m^3	7 h/d, 5 d/week, up to 24 months	UICC, milled UICC, unmilled: 52.6% >5 μm	7/126 (0 MM)	0/24 MM	1/24 MM	(Wagner, 1990; Wagner et al., 1974)
Mode of delivery: intrapleural								
CH	Rat	0.5–8 mg	Single dose	UICC: 3750 f/cc >5 μm Grade 7: 1020 f/cc >5 μm SFA: 430 f/cc >5 μm	Saline: 0 MM	SFA: 18/48 MM Grade 7: 13/48 MM	UICC: 5/48 MM	(Wagner et al., 1980)
CR	Rat	40 mg	Single dose	**Common log f/μg; L ≥ 8 μm, D ≤ 0.25 μm** CR 1: 5.21; CR 2: 4.30 CR 3: 5.01; CR 4: 5.13 CR 5: 3.29; CR 6: 14.6 CR 7: 2.65; CR 8: 0 CR 9: 4.25; CR 10: 3.09 CR 11: 0; CR 12: 3.73 CR 13: 0	NR	**Tumor incidence (probability)** CR 8: 8/25 (53 ± 12.9) CR 11: 4/29 (19 ± 8.5) CR 13: 0/29 (0)	**Tumor incidence (probability)** CR 1: 18/27 (94 ± 6.0) CR 2: 17/24 (93 ± 6.5) CR 3: 15/23 (93 ± 6.9) CR 4: 15/24 (86 ± 9.0) CR 5: 14/29 (78 ± 10.8) CR 6: 9/27 (63 ± 13.9) CR 7: 11/26 (56 ± 11.7) CR 9: 8/27 (33 ± 9.8) CR 10: 6/29 (37 ± 13.5) CR 12: 2/27 (10 ± 7.0)	(Stanton et al., 1981)
CR	Rat	20 mg	Single dose	Unmilled: 61.0 fib ≥6.5 μm Milled 2 h: 23.3 fib ≥6.5 μm Milled 4 h: 4.25 fib ≥6.5 μm Milled 8 h: 8.5 fib ≥6.5 μm	Saline: 1/40 MM	Milled 2 h: 34 (81%) MM Milled 4 h: 15 (37%) MM Milled 8 h: 13 (31%) MM	Unmilled: 35 (85%) MM	(Wagner et al., 1984, 1985)
Mode of delivery: intraperitoneal								
AM	Rat	10–25 mg	Single dose	Short: 1% >5 μm Long: 30% >5 μm	NR	10 mg: 0/24 MM 20 mg: 1/24 MM	10 mg: 21/24 MM 20 mg: 20/24 MM	(Davis et al., 1986b)
CH	Rat	25 mg	4 injections	Milled Unmilled	8 abdominal tumors	5/16 abdominal tumors	16/40 abdominal tumors	(Pott et al., 1972)
CH	Rat	25 mg	4 injections	Milled: 99.8% <5 μm Unmilled: 93.9% <5 μm	Saline: 0/40 (0%)	12/40 (30%)	15/40 (37.5%)	(Pott et al., 1974)
CH	Rat	25 mg	4 injections	Milled: 99.8% <5 μm Unmilled: 93.9% <5 μm	Saline: 0/72 tumors	12/37 tumors (9 MM)	18/33 tumors (16 MM)	(Pott et al., 1976)
CH	Rat	0.25–25 mg	Single dose	Short: 2.3% >8 μm Long: 10.2% >8 μm	NR	0.25 mg: 0/24 MM 2.5 mg: 8/24 MM 25 mg: 22/24 MM	0.25 mg: 16/24 MM 2.5 mg: 22/24 MM 25 mg: 23/24 MM	(Davis & Jones, 1988)
CH	Rat	1 mg	2 injections; 1/week	UICC B: long Calidria: short	NR	1 mg: 1/50 MM	1 mg: 31/50 MM	(Rittinghausen et al., 1991)

AM: amosite; AN: anthophyllite; CH: chrysotile; CR: crocidolite; TR: tremolite; MM: mesothelioma; NR: not reported.

presence of asbestos bodies (Platek et al., 1985; Stettler et al., 2008).

In vitro *cell culture studies*

In vitro cell culture studies are useful when comparing the effects of different mineral properties (e.g. chemical composition, size, morphology) with markers predictive of pathogenicity, such as toxicity and proliferation. The major limitation associated with *in vitro* studies is that these do not mimic human exposure. *In vitro* cell systems are often comprised of a monolayer of one type of immortalized cells rather than the three-dimensional, multi-cellular and biochemical interactive structure that exists in the human body. Furthermore, many of the *in vitro* studies were conducted with concentrations significantly higher than those that occur at the target tissue following human occupational and environmental exposure. Nevertheless, *in vitro* studies can be powerful tools for understanding mechanisms of toxicity. Table 3 presents a summary of *in vitro* studies that directly compared short and long asbestos fiber preparations. Collectively, the weight of evidence from mechanistic studies on cells in culture suggests the toxicity, mutagenicity, and proliferative potential of the fibers increase with increasing length.

Deposition and retention in relation to fiber length

Human studies

Several groups have documented fiber concentration and size retained in the lung tissue of those occupationally exposed to asbestos (Churg & Wiggs, 1984, 1986, 1987; Langer & Nolan, 1994; Suzuki & Yuen, 2002; Tossavainen et al., 1994). These groups reported that shorter fibers were more abundant in the human lung of those occupationally exposed to asbestos than longer fibers, regardless of fiber type. One group suggested, based on these data, that either the carcinogenic size range is much broader than thought or a small number of fibers in certain size ranges can induce tumors in humans (Churg & Wiggs, 1984). Additionally, it has been suggested that the choice of which sizes to measure favored the selection and counting of shorter fibers, and therefore may have underrepresented the longer fibers in the counting process (Becklake & Case, 1994).

It is important to note the differences in biopersistence between chrysotile and amphibole asbestos when assessing lung fiber burden. Clearance and biopersistence contribute to fiber burden such that failed clearance and durability of the fiber can increase the retention time of the fiber. Chrysotile fibers are readily depleted of critical components of their structure (e.g. Mg) in the lung milieu, thereby weakening the fibers resulting in either fragmentation of longer fibers or dissolution (Jaurand et al., 1977). Amphibole fibers are far more resistant to this type of leaching and fragmentation (Hesterberg et al., 1998; Jaurand et al., 1977; Roggli & Brody, 1984). Therefore, there is less accumulation of the effective dose of long chrysotile fibers than for long amphibole fibers.

Although lung burden analysis in humans is a good marker for past exposure, it is a poor index of dose and fiber characteristics. It represents only what remains following the period from the last exposure, which can be decades. As such, knowledge of the kinetics of fiber deposition and clearance comes primarily from rodent studies, which are discussed below.

Animal studies

Short fibers (<5 μm) may be less pathogenic because of their decreased deposition or penetration into the airways, and increased clearance by macrophages and other cell types (reviewed in HEI-AR, 1991). Results from animal bioassays conducted over the course of the last 40 years have demonstrated that approximately 90% of inhaled asbestos fibers deposited in the lung are between 5 and 10 μm in length and that deposition decreases (at constant fiber diameter) as fiber length increases (Hammad et al., 1982; Morgan et al., 1978, 1980; Timbrell, 1965; Timbrell et al., 1970). Timbrell (1965) was the first to investigate how fiber dimension impacts fiber deposition when they demonstrated through physical analyses that the falling speed of glass fibers was dependent more on fiber diameter than length. The authors suggested that these results provided an explanation for observations made by others that asbestos fibers up to 200 μm in length can be deposited. In 1995, Morgan reviewed the literature relating to fiber length and deposition and suggested that very long fibers can penetrate to and be deposited in the alveolar region of the human lung, provided that they are straight (Morgan, 1995). Morgan concluded that total deposition increases with fiber length, but both lower respiratory tract and alveolar deposition decline with increasing fiber length.

The available data suggest that short asbestos fibers (<5 μm) are cleared more efficiently than longer asbestos fibers (>20 μm), with a half-life of approximately 10 days for fibers 0.4–4 μm in length and approximately 114 days for fibers greater than 16 μm in length (Coin et al., 1992; Morgan et al., 1978). These observations in clearance half-lives are strongly governed by the functionality of natural defense mechanisms within the lung, such as phagocytosis, which are easily overcome by longer length fibers (Snipes, 1995). Consequently, shorter fibers have a tendency to dissolve more rapidly than longer fibers, as shorter fibers have a greater surface area and are effectively exposed to the low pH environment of macrophage lysosomes (Coin et al., 1992; Searl et al., 1999; Snipes, 1995). Based on modeling results, Berry found that the influence of solubility of fibers on the mesothelioma rate is 17 times higher in the human than in the rat principally because rats age and develop cancer at a much higher rate (Berry, 1999). Thus, the author suggested that this implies that relatively soluble fibers that do not produce disease in rats are even less likely to do so in humans.

Recent research has shown that fiber length and biopersistence can influence clearance of fibers through the pleural stomata opening and prevent clearance via the lymphatic

Table 3. *In vitro* studies in which fiber length was considered.

Cell culture model	Type of asbestos	Particle length	Exposure concentration	Exposure duration	Type of assays	Summary	Study
Rodent models							
Rat phagocytic ascetic tumor cells	AM; CH; CR	Ultrafine: 3 μm Fine: 8 μm Modified: 50 μm	30 μg/mL	72 h	DNA and protein synthesis; cytotoxicity	Noted that the toxicity of the fibers increased with increasing length regardless of fiber type.	(Tilkes & Beck, 1980)
Mouse peritoneal macrophages	AM; CH; CR	UICC: ultrafine; medium; long	100 μg/1.5 × 10^6 cells	72 h	Erythrosin uptake; cytotoxicity	Concluded that short fibers were less cytotoxic than long fibers when used on the basis of equal mass.	(Kaw et al., 1982)
Hamster tracheal organ culture	CH	Short: 100% ≤5 μm Long: 0% ≤5 μm	1–16 mg/mL	1 h	Assessment of metaplasia	While short fibers did not stimulate cell proliferation, long chrysotile fibers induced cell distortion and sloughing. Both long and short fibers induced a significant increase in metaplasia at low doses.	(Woodworth et al., 1983)
Guinea pig lung macrophages	CH; CR	CH Short Munroe: 0.4–9.99 μm CH Long Munroe: <3–80 μm CH Jeffrey 1: 1–19 μm CH Jeffery 2: 0.1–39 μm CR Short: 0.1–19 μm CR Short S. African: 0.4–29 μm CR Long: 3–129 μm	100 μg/10^6 cells	20 h	Cytotoxicity; phagocytic activity	Found that long, thin fibers were toxic regardless of fiber type.	(Tilkes & Beck, 1983)
Rat peritoneal macrophages	AM	Short: 0.5% >5 μm UICC: 9.5% >5 μm Long: 31% >5 μm	200 μg/mL	48 or 96 h	Collagen protein synthesis	All fiber types induced production or release of fibrogenic factor, however short fibers were more active than long fibers.	(Aalto & Heppleston, 1984)
Syrian hamster embryo cells	CH	Unmilled: 10–16 μm Milled: 1.7 μm	0.25–2 μg/cm^2	7 days	Cytotoxicity; morphological transformation	After milling of fibers to reduce the length from 10 to 16 microns to less than 1.7 μm while the diameter remained the same, morphologic transformation, an indication of tumorigenic potential, is completely inhibited. At all doses, the transforming potency of SHE cells by the chrysotile asbestos was eliminated.	(Hesterberg & Barrett, 1984)
Hamster tracheal epithelial cells	CH	Short: ≤2 μm Long: ≥10 μm	0.65–5.8 μg/cm^2	24 h	ODC activity	Maximal elevation of ODC activity was observed after exposure of cells to very low concentrations (0.72 μg/cm^2 dish) of long fibers, whereas a four-fold higher concentration (2.9 μg/cm^2 dish) of short fibers was required to induce similar effects. Potency of ODC induction was directly related to fiber length.	(Marsh & Mossman, 1988)
Peritoneal macrophages	CR	Short: 0% >8 μm Mixed: 5% >8 μm Long: 14.8% >8 μm	5–1000 μg	Up to 22 h	Cell viability; H_2O_2 production; mitochondrial membrane potential	The release of reactive oxygen species was stimulated by both long and short crocidolite; however, long fibers were found to be more toxic than short fibers.	(Goodglick & Kane, 1990)

(*continued*)

Table 3. Continued

Cell culture model	Type of asbestos	Particle length	Exposure concentration	Exposure duration	Type of assays	Summary	Study
Rat alveolar macrophages	AM	Short: ~100% <10 μm Long: 40% >10 μm	10–50 μg/mL	24 h	Cytotoxicity; cell viability	Short fibers were not effective at stimulating release of TNF-α while high doses of long fibers significantly increased the release of TNF-α following exposure to amosite.	(Dogra & Donaldson, 1995)
Chinese hamster ovary cells	AM	Short: 10% >10 μm Long: 70% >10 μm	10 μg/mL	48 h	Chromosomal aberrations and hyperploidy	Long amosite fibers significantly increased the incidence of chromosomal aberrations while the incidence of chromosomal aberrations in these cultures following treatment with short fiber amosite was similar to controls. Cells exposed to long amosite also demonstrated significantly less mitotic index.	(Donaldson & Golyasnya, 1995)
Rat alveolar macrophages	AM	Short: ~100% <10 μm Long: 40% >10 μm	1 mg/mL	30 minutes	Assay of superoxide anions	A dramatic enhancement of superoxide anion release was observed with long, but not short amosite fibers following opsonization. Short fibers induced superoxide anion release significantly above background.	(Hill et al., 1995)
Primate models							
Human alveolar macrophages	CH	UICC Rhodesian: 75% <5 μm Unmilled RG 144: 98% <5 μm Milled RG 144: 99–100% <5 μm	50–100 μg	24 h	Cytotoxicity	Viability of the cells following treatment was 67% for UICC chrysotile, 47% for unmilled RG 144 chrysotile, and 24–40% for milled RG 144 chrysotile, suggesting that the increase in fiber number and total surface area may explain enhanced cytotoxicity of the milled asbestos.	(Yeager et al., 1983)
Human type 2 alveolar epithelial cells	AM	Short: <10% >10 μm Long: 70% >10 μm	10–100 μg/mL	4 h	Epithelial cell injury assay	Long fibers caused rapid detachment relative to the short fiber preparation.	(Donaldson et al., 1993)
Human lung epithelial cells	AM	Short: 98% <5 μm Long: 7 0% <5 μm	0.35–35 μg/cm^2	24 h	Measurement of PPP activity; lipid peroxidation assay; cytotoxicity; enzyme activity assay	Long amosite fibers initiated free radical reactions, significantly inhibited glucose-6-phosphate dehydrogenase (G6PD) and PPP activity, decreased intracellular glutathione and increased thiobarbituric acid reactive substances and leakage of lactase dehydrogenase more effectively than short amosite.	(Riganti et al., 2003)

AM: amosite; CH: chrysotile; CR: crocidolite; LDH: lactate dehydrogenase; ODC: ornithine decarboxylase; PPP: pentose phosphate pathway.

system (Donaldson et al., 2010; Murphy et al., 2011; Osmond-McLeod et al., 2011). Recent studies by Donaldson et al. have provided additional insights as to how biodurable, biopersistent long asbestos fibers induce effects on the pleura. As evidenced by "black spots" on the parietal pleural wall at autopsy of urban dwellers, a fraction of all deposited particles reach the pleura and through normal pathways of clearance exit the pleura through stomata in the parietal pleura. The stomatal openings on the parietal pleura drain fluid from the pleural space into lung lymph nodes. Donaldson et al. hypothesized that if particles are too large or too elongated to navigate through the stomatal opening, accumulation can occur leading to inflammation and pleural pathology, including mesothelioma (Donaldson et al., 2010). While the impetus for this original hypothesis and recent research was to explore how HARN, such as carbon nanotubes, may fit into the classic fiber toxicology paradigm, the emphasis of retention of biodurable long fibers on the parietal pleura also has implications for understanding the origins of asbestos-related diseases (Donaldson et al., 2010).

Conclusions

Evidence demonstrating that fiber length is a key factor in pathogenicity of fibers comes from a number of sources, but the best data are from animal studies where it is possible to segregate fiber populations by length and assess their effects, unlike the mixed nature of human exposures. Ultimately, the size of a fiber determines its residence time in the lung. Longer fibers have been shown to be more harmful because they cannot easily be engulfed by alveolar macrophages, the cells responsible for breaking down asbestos fibers in the terminal air spaces of the lungs. This results in a phenomenon known as incomplete phagocytosis, which prevents efficient clearance of fibers from the lungs (Barlow et al., 2013). Fibers retained in the lungs can cause injury to epithelial or mesothelial cells, primarily through a process initiated by the release of various pro-inflammatory factors and reactive oxygen species released by activated macrophages (Barlow et al., 2013).

Over the past 30 years, there have been numerous differing views on the degree to which chemical and crystalline composition, fiber dimension, aerodynamic characteristics and/or biodurability influence the potential toxicity of serpentine asbestos relative to amphibole asbestos (ACGIH, 1980; Berman & Crump, 2003, 2008a, 2008b; Bernstein & Hoskins, 2006; Bernstein et al., 2013; Gibbs & Berry, 2008; Hodgson & Darnton, 2000; Hodgson et al., 2005). Although one should take into account fiber length when considering the potential toxicological properties of asbestos fibers, it is apparent that it cannot be the only metric relied upon in determining risk. Often, exposure to even significant doses of chrysotile asbestos does not increase the incidence of cancer in a particular cohort (Pierce et al., 2016), while exposure to lower concentrations of another form of asbestos (i.e. amphibole) can significantly affect the cancer rate in exposed cohorts (Berman & Crump, 2008b; Hodgson & Darnton, 2000). Multiple factors including the tumor type, animal system examined, available toxicological data and epidemiological data need to be considered when attempting to predict whether a specific agent poses a significant hazard to humans at doses to which they might reasonably be exposed.

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All of the authors are employed by Cardno ChemRisk, a consulting firm that provides scientific advice to the government, corporations, law firms and various scientific/professional organizations. This manuscript was prepared and written exclusively by the authors. No outside financial support was provided to any of the authors for preparing the manuscript. One of the authors (C.A.B.) has served as an expert in asbestos-related litigation. It is likely that this work will be relied upon in occupational health and exposure assessment research and asbestos-related litigation.

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References

Aalto M, Heppleston AG. (1984). Fibrogenesis by mineral fibres: an in-vitro study of the roles of the macrophage and fibre length. Br J Exp Pathol 65:91–9.

ACGIH. (1980). Asbestos. In: ACGIH (ed.) American Conference of Governmental Industrial Hygienists, Documentation of the Threshold Limit Values: For Chemical Substances in the Workroom Environment. 4th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 27–30.

Adamson IY, Bakowska J, Bowden DH. (1993). Mesothelial cell proliferation after instillation of long or short asbestos fibers into mouse lung. Am J Pathol 142:1209–16.

Adamson IY, Bowden DH. (1987a). Response of mouse lung to crocidolite asbestos. 1. Minimal fibrotic reaction to short fibres. J Pathol 152:99–107.

Adamson IY, Bowden DH. (1987b). Response of mouse lung to crocidolite asbestos. 2. Pulmonary fibrosis after long fibres. J Pathol 152:109–17.

ATSDR. (2002). Expert Panel on Health Effects of Asbestos and Synthetic Vitreous Fibers (SVF): The Influence of Fiber Length. Premeeting Comments; 2002 Oct 29–30; New York, NY. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Barlow CA, Lievense L, Gross S, et al. (2013). The role of genotoxicity in asbestos-induced mesothelioma: an explanation for the differences in carcinogenic potential among fiber types. Inhal Toxicol 25:553–67.

Becklake MR, Case BW. (1994). Fiber burden and asbestos-related lung disease: determinants of dose–response relationships. Am J Respir Crit Care Med 150:1488–92.

Berman DW, Crump KS. (2003). Final draft: technical support document for a protocol to assess asbestos-related risk. EPA# 9345.4-06; October 2003. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

Berman DW, Crump KS. (2008a). A meta-analysis of asbestos-related cancer risk that addresses fiber size and mineral type. Crit Rev Toxicol 38(Suppl. 1): 49–73.

Berman DW, Crump KS. (2008b). Update of potency factors for asbestos-related lung cancer and mesothelioma. Crit Rev Toxicol 38(Suppl. 1): 1–47.

Berman DW, Crump KS, Chatfield EJ, et al. (1995). The sizes, shapes, and mineralogy of asbestos structures that induce lung tumors or mesothelioma in AF/HAN rats following inhalation. Risk Anal 15:181–95. Erratum in: Risk Anal 15:541.

Bernstein D, Dunnigan J, Hesterberg T, et al. (2013). Health risk of chrysotile revisited. Crit Rev Toxicol 43:154–83.
Bernstein DM, Hoskins JA. (2006). The health effects of chrysotile: current perspective based upon recent data. Regul Toxicol Pharmacol 45:252–64.
Berry G. (1999). Models for mesothelioma incidence following exposure to fibers in terms of timing and duration of exposure and the biopersistence of the fibers. Inhal Toxicol 11:111–30.
Brain JD, Knudson DE, Sorokin SP, Davis MA. (1976). Pulmonary distribution of particles given by intratracheal instillation or by aerosol inhalation. Environ Res 11:13–33.
Burger BF, Engelbrecht FM. (1970a). The biological effects of the international standard reference asbestos samples on the lungs of rats. South Afr J Lab Clin Med 16:1271–4.
Burger BF, Englebrecht FM. (1970b). The biological effects of long and short fibers of crocidolite and chrysolite a after intra pleural injection into rats. South Afr J Lab Clin Med 16:1268–70.
Churg A, Wiggs B. (1984). Fiber size and number in amphibole asbestos-induced mesothelioma. Am J Pathol 115:437–42.
Churg A, Wiggs B. (1986). Fiber size and number in workers exposed to processed chrysotile asbestos, chrysotile miners, and the general population. Am J Ind Med 9:143–52.
Churg A, Wiggs B. (1987). Types, numbers, sizes, and distribution of mineral particles in the lungs of urban male cigarette smokers. Environ Res 42:121–9.
Coin PG, Roggli VL, Brody AR. (1992). Deposition, clearance, and translocation of chrysotile asbestos from peripheral and central regions of the rat lung. Environ Res 58:97–116.
Cossette M, Delvaux P. (1979). Technical evaluation of chrysotile asbestos ore bodies. Short Course Mineral Techn Asbestos Determin 4:79–109.
Crapo JD, Barry BE, Brody AR, O'Neil JJ. (1980). Morphological, morphometric and X-ray microanalytical studies on lung tissue of rats exposed to chrysotile asbestos in inhalation chambres. IARC Sci Publ 30:273–83.
Davis JM. (1972). The fibrogenic effects of mineral dusts injected into the pleural cavity of mice. Br J Exp Pathol 53:190–201.
Davis JM, Addison J, Bolton RE, et al. (1985). Inhalation studies on the effects of tremolite and brucite dust in rats. Carcinogenesis 6:667–74.
Davis JM, Addison J, Bolton RE, et al. (1986a). Inhalation and injection studies in rats using dust samples from chrysotile asbestos prepared by a wet dispersion process. Br J Exp Pathol 67:113–29.
Davis JM, Addison J, Bolton RE, et al. (1986b). The pathogenicity of long versus short fibre samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. Br J Exp Pathol 67:415–30.
Davis JM, Beckett ST, Bolton RE, Donaldson K. (1980). A comparison of the pathological effects in rats of the UICC reference samples of amosite and chrysotile with those of amosite and chrysotile collected from the factory environment. IARC Sci Publ 92:285–92.
Davis JM, Beckett ST, Bolton RE, et al. (1978). Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. Br J Cancer 37:673–88.
Davis JM, Jones AD. (1988). Comparisons of the pathogenicity of long and short fibres of chrysotile asbestos in rats. Br J Exp Pathol 69:717–37.
Dement JM, Brown DP, Okun A. (1994). Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. Am J Ind Med 26:431–47.
Dement JM, Harris RL, Jr., Symons MJ, Shy C. (1982). Estimates of dose–response for respiratory cancer among chrysotile asbestos textile workers. Ann Occup Hyg 26:869–87.
Dement JM, Kuempel ED, Zumwalde RD, et al. (2008). Development of a fibre size-specific job-exposure matrix for airborne asbestos fibres. Occup Environ Med 65:605–12.
Dement JM, Myers D, Loomis D, et al. (2009). Estimates of historical exposures by phase contrast and transmission electron microscopy in North Carolina USA asbestos textile plants. Occup Environ Med 66:574–83.
Dodson RF, Atkinson MA, Levin JL. (2003). Asbestos fiber length as related to potential pathogenicity: a critical review. Am J Ind Med 44:291–7.
Dogra S, Donaldson K. (1995). Effect of long and short fibre amosite asbestos on in vitro TNF production by rat alveolar macrophages: the modifying effect of lipopolysaccharide. Ind Health 33:131–41.
Doll R, Peto J. (1985). Asbestos: effects on health of exposure to asbestos. London: Her Majesty's Stationary Office.
Donaldson K, Brown GM, Brown DM, et al. (1989). Inflammation generating potential of long and short fibre amosite asbestos samples. Br J Ind Med 46:271–6.
Donaldson K, Golyasnya N. (1995). Cytogenetic and pathogenic effects of long and short amosite asbestos. J Pathol 177:303–7.
Donaldson K, Miller BG, Sara E, et al. (1993). Asbestos fibre length-dependent detachment injury to alveolar epithelial cells in vitro: role of a fibronectin-binding receptor. Int J Exp Pathol 74:243–50.
Donaldson K, Murphy FA, Duffin R, Poland CA. (2010). Asbestos, carbon nanotubes and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma. Part Fibre Toxicol 7:5.
Driscoll KE. (2000). TNFalpha and MIP-2: role in particle-induced inflammation and regulation by oxidative stress. Toxicol Lett 112–113:177–83.
ERG. (2003a). Report on the expert panel on health effects of asbestos and synthetic vitreous fibers: the influence of fiber length. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Division of Health Assessment and Consultation.
ERG. (2003b). Report on the peer consultation workshop to discuss a proposed protocol to assess asbestos-related risk. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency.
Garabrant DH, Alexander DD, Miller PE, et al. (2016). Mesothelioma among motor vehicle mechanics: an updated review and meta-analysis. Ann Occup Hyg 60:8–26.
Gibbs GW, Berry G. (2008). Mesothelioma and asbestos. Regul Toxicol Pharmacol 52:S223–S31.
Goodglick LA, Kane AB. (1990). Cytotoxicity of long and short crocidolite asbestos fibers in vitro and in vivo. Cancer Res 50:5153–63.
Hammad Y, Diem J, Craighead J, Weill H. (1982). Deposition of inhaled man-made mineral fibres in the lungs of rats. Ann Occup Hyg 26:179–87.
HEI-AR. (1991). Asbestos in public and commercial buildings: a literature review and synthesis of current knowledge. Cambridge, MA: Health Effects Institute-Asbestos Research.
Hesterberg TW, Barrett JC. (1984). Dependence of asbestos- and mineral dust-induced transformation of mammalian cells in culture on fiber dimension. Cancer Res 44:2170–80.
Hesterberg TW, Chase G, Axten C, et al. (1998). Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. Toxicol Appl Pharmacol 151:262–75. Erratum in: Toxicol Appl Pharmacol 155:292 (1999 Mar 15).
Hill IM, Beswick PH, Donaldson K. (1995). Differential release of superoxide anions by macrophages treated with long and short fibre amosite asbestos is a consequence of differential affinity for opsonin. Occup Environ Med 52:92–6.
Hodgson JT, Darnton A. (2000). The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. Ann Occup Hyg 44:565–601.
Hodgson JT, McElvenny DM, Darnton AJ, et al. (2005). The expected burden of mesothelioma mortality in Great Britain from 2002 to 2050. Br J Can 92:587–93.
Hughes JM, Weill H. (1986). Asbestos exposure-quantitative assessment of risk. Am Rev Respir Dis 133:5–13.
Huncharek M. (1987). Chrysotile asbestos exposure and mesothelioma. Br J Ind Med 44:287–8.
Hurbankova M, Kaiglova A. (1997). Some bronchoalveolar lavage parameters and leukocyte cytokine release in response to intratracheal instillation of short and long asbestos and wollastonite fibres in rats. Physiol Res 46:459–66.

Ilgren EB. (2002). Coalinga fibre: a short-fibre, amphibole-free chrysotile. Indoor Built Environ 11:171–7.
Ilgren E, Chatfield E. (1998a). Coalinga fibre: a short, amphibole-free chrysotile. Part 2: evidence for lack of tumourigenic activity. Indoor Built Environ 7:18–31.
Ilgren E, Chatfield E. (1998b). Coalinga fibre: a short, amphibole-free chrysotile: Part 3: lack of biopersistence. Indoor Built Environ 7:98–109.
Ilgren E, Chatfield E. (1997). Coalinga fibre: a short, amphibolic-free chrysotile. Part 1: evidence for lack of fibrogenic activity. Indoor Built Environ 6:264–76.
Jaurand MC, Bignon J, Sebastien P, Goni J. (1977). Leaching of chrysotile asbestos in human lungs. Correlation with in vitro studies using rabbit alveolar macrophages. Environ Res 14:245–54.
Kaw JL, Tilkes F, Beck EG. (1982). Reaction of cells cultured in vitro to different asbestos dusts of equal surface area but different fibre length. Br J Exp Pathol 63:109–15.
King EJ, Clegg JW, Rae VM. (1946). The effect of asbestos, and of asbestos and aluminium, on the lungs of rabbits. Thorax 1:188–97.
Kuschner M, Wright G. (1976). The effects of intratracheal instillation of glass fiber of varying sizes in guinea pigs. In: NIOSH (ed.) Occupational Exposure to Fibrous Glass: Proceedings of a Symposium; 1976 Apr. Washington, DC: U.S. Dept. of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 151–68.
Laden F, Stampfer MJ, Walker AM. (2004). Lung cancer and mesothelioma among male automobile mechanics: a review. Rev Environ Health 19:39–61.
Langer AM, Nolan RP. (1994). Chrysotile biopersistence in the lungs of persons in the general population and exposed workers. Environ Health Perspect 102(Suppl. 5): 235–9.
Lemaire I, Nadeau D, Dunnigan J, Masse S. (1985). An assessment of the fibrogenic potential of very short 4T30 chrysotile by intratracheal instillation in rats. Environ Res 36:314–26.
Lippmann M. (1988). Asbestos exposure indices. Environ Res 46:86–106.
Lippmann M. (1994). Deposition and retention of inhaled fibres: effects on incidence of lung cancer and mesothelioma. Occup Environ Med 51:793–8.
Loomis D, Dement JM, Elliott L, et al. (2012). Increased lung cancer mortality among chrysotile asbestos textile workers is more strongly associated with exposure to long thin fibres. Occup Environ Med 69:564–8.
Mann EL. (1983). Asbestos. In: Lefond SJ (ed) Industrial minerals and rocks. 5th ed. New York: Society Mining Engineers of the American Institute of Mining, Metallurgical, and Petroleum Engineers, 435–84.
Marsh JP, Mossman BT. (1988). Mechanisms of induction of ornithine decarboxylase activity in tracheal epithelial cells by asbestiform minerals. Cancer Res 48:709–14.
McDonald AD, Fry JS, Woolley AJ, McDonald J. (1983a). Dust exposure and mortality in an American chrysotile textile plant. Br J Ind Med 40:361–7.
McDonald AD, Fry JS, Woolley AJ, McDonald JC. (1983b). Dust exposure and mortality in an American factory using chrysotile, amosite, and crocidolite in mainly textile manufacture. Br J Ind Med 40:368–74.
Meldrum M. (1996). Review of fibre toxicology. Sudbury: HSE Books, HMSO.
Miller BG, Jones AD, Searl A, et al. (1999). Influence of characteristics of inhaled fibres on development of tumours in the rat lung. Ann Occup Hyg 43:167–79.
Morgan A. (1995). Deposition of inhaled asbestos and man-made mineral fibres in the respiratory tract. Ann Occup Hyg 39:747–58.
Morgan A, Black A, Evans N, et al. (1980). Deposition of sized glass fibres in the respiratory tract of the rat. Ann Occup Hyg 23:353–66.
Morgan A, Talbot RJ, Holmes A. (1978). Significance of fibre length in the clearance of asbestos fibres from the lung. Br J Ind Med 35:146–53.
Mossman BT, Lippmann M, Hesterberg TW, et al. (2011). Pulmonary endpoints (lung carcinomas and asbestosis) following inhalation exposure to asbestos. J Toxicol Environ Health B Crit Rev 14:76–121.
Murphy FA, Poland CA, Duffin R, et al. (2011). Length-dependent retention of carbon nanotubes in the pleural space of mice initiates sustained inflammation and progressive fibrosis on the parietal pleura. Am J Pathol 178:2587–600.
Nicholson WJ. (1991). Comparative dose–response relationship of asbestos fiber types: magnitudes and uncertainties. Ann NY Acad Sci 643:74–84.
Nicholson WJ, Landrigan PJ. (1994). The carcinogenicity of chrysotile asbestos. Advances in modern environmental toxicology (volume 22): the identification and control of environmental and occupational diseases: asbestos and cancer. Princeton, NJ: Princeton Scientific Publishing Co., 407–23.
Nicholson WJ, Landrigan PJ. (1996). Asbestos: a status report. Curr Issues Public Health 2:118–23.
Nicholson WJ, Raffn E. (1995). Recent data on cancer due to asbestos in the USA and Denmark. Med Lav 86:393–410.
Nicholson WJ. (2001). The carcinogenicity of chrysotile asbestos—a review. Ind Health 39:57–64.
Oberdorster G. (1995). Lung particle overload: implications for occupational exposures to particles. Regul Toxicol Pharmacol 27:123–35.
Osmond-McLeod MJ, Poland CA, Murphy F, et al. (2011). Durability and inflammogenic impact of carbon nanotubes compared with asbestos fibres. Part Fibre Toxicol 8:15.
Pierce JS, Ruestow PS, Finley BL. (2016). An updated evaluation of reported no-observed adverse effect levels for chrysotile asbestos for lung cancer and mesothelioma. Crit Rev Toxicol 46:561–86.
Pigg BJ. (1994). The uses of chrysotile. Ann Occup Hyg 38:453–8.
Platek SF, Groth DH, Ulrich CE, et al. (1985). Chronic inhalation of short asbestos fibers. Fundam App Toxicol 5:327–40.
Pott F. (1978). Some aspects on the dosimetry of the carcinogenic potency of asbestos and other fibrous dusts. Straub-Reinhalt Luft 38:486–90.
Pott F, Friedrichs KH, Huth F. (1976). Results of animal experiments concerning the carcinogenic effect of fibrous dusts and their interpretation with regard to the carcinogenesis in humans (author's transl). Zentralbl Bakteriol Orig B 162:467–505.
Pott F, Huth F, Friedrichs KH. (1972). Tumors of rats after i.p. injection of powdered chrysotile and benzo(a)pyrene. Zentralbl Bakteriol Orig B 155:463–9.
Pott F, Huth F, Friedrichs KH. (1974). Tumorigenic effect of fibrous dusts in experimental animals. Environ Health Perspect 9:313–5.
Riganti C, Aldieri E, Bergandi L, et al. (2003). Long and short fiber amosite asbestos alters at a different extent the redox metabolism in human lung epithelial cells. Toxicol Appl Pharmacol 193:106–15.
Rittinghausen S, Ernst H, Muhle H, et al. (1991). Histopathological analysis of tumour types after intraperitoneal injections of mineral fibres in rats. In: Brown, RC, Hoskins, JA, Johnson, NF (eds.) Mechanisms in fibre carcinogenesis. Albuquerque: NATO ASI Series, 81–9.
Roggli VL, Brody AR. (1984). Changes in numbers and dimensions of chrysotile asbestos fibers in lungs of rats following short-term exposure. Exp Lung Res 7:133–47.
Searl A, Buchanan D, Cullen RT, et al. (1999). Biopersistence and durability of nine mineral fibre types in rat lungs over 12 months. Ann Occup Hyg 43:143–53.
Smith JM, Wootton ID, King EJ. (1951). Experimental asbestosis in rats. The effect of particle size and of added alumina. Thorax 6:127–36.
Snipes MB. (1995). Pulmonary retention of particles and fibres: biokinetics and effects of exposure concentrations. In: MacClellan RO, Henderson RF (eds.) Concepts in inhalation toxicology. 2nd ed. Washington, DC: Taylor & Francis, 225–55.
Stanton MF. (1973). Some etiological considerations of fibre carcinogenesis. In: Bogovski P, Timbrell V, Gilson JC, Wagner JC (eds.) Biological Effects of Asbestos: Proceedings of a Working Conference. IARC Scientific Publications No. 8. Lyon: International Agency for Research on Cancer, 289–94.

Stanton MF, Layard M, Tegeris A, et al. (1977). Carcinogenicity of fibrous glass: pleural response in the rat in relation to fiber dimension. J Natl Cancer Inst 58:587–603.

Stanton MF, Layard M, Tegeris A, et al. (1981). Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl Cancer Inst 67:965–75.

Stanton MF, Wrench C. (1972). Mechanisms of mesothelioma induction with asbestos and fibrous glass. J Natl Cancer Inst 48:797–821.

Stettler LE, Sharpnack DD, Krieg EF. (2008). Chronic inhalation of short asbestos: lung fiber burdens and histopathology for monkeys maintained for 11.5 years after exposure. Inhal Toxicol 20:63–73.

Suzuki Y, Yuen SR. (2001). Asbestos tissue burden study on human malignant mesothelioma. Ind Health 39:150–60.

Suzuki Y, Yuen SR. (2002). Asbestos fibers contributing to the induction of human malignant mesothelioma. Ann NY Acad Sci 982:160–76.

Suzuki Y, Yuen SR, Ashley R. (2005). Short, thin asbestos fibers contribute to the development of human malignant mesothelioma: pathological evidence. Int J Hyg Environ Health 208:201–10.

Tilkes F, Beck EG. (1980). Comparison of length-dependent cytotoxicity of inhalable asbestos and man-made mineral fibres. IARC Sci Publ 30:475–83.

Tilkes F, Beck EG. (1983). Macrophage functions after exposure to mineral fibers. Environ Health Perspect 51:67–72.

Timbrell V. (1965). Human exposure to asbestos: dust controls and standards. The inhalation of fibrous dusts. Ann N Y Acad Sci 132:255–73.

Timbrell V, Bevan NE, Davies AS, Munday DE. (1970). Hollow casts of lungs for experimental purposes. Nature 225:97–8.

Tossavainen A, Karjalainen A, Karhunen PJ. (1994). Retention of asbestos fibers in the human body. Environ Health Perspect 102(Suppl. 5):253–5.

Vorwald AJ, Durkan TM, Pratt PC. (1951). Experimental studies of asbestosis. AMA Arch Ind Hyg Occup Med 3:1–43.

Wagner JC. (1990). Biological effects of short fibers. Proceedings of the VIIth International Pneumoconiosis Conference Part II, November. DHHS (NIOSH) Publication No. 90-108 Part II. Animal Models-Pneumoconiosis II; 1990 Nov. Washington, DC: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, 835–9.

Wagner JC, Berry G, Skidmore JW, Pooley FD. (1980). The comparative effects of three chrysotiles by injection and inhalation in rats. IARC Sci Publ 92:363–72.

Wagner JC, Berry G, Skidmore JW, Timbrell V. (1974). The effects of the inhalation of asbestos in rats. Br J Cancer 29:252–69.

Wagner JC, Griffiths DM, Hill RJ. (1984). The effect of fibre size on the in vivo activity of UICC crocidolite. Br J Cancer 49:453–8.

Wagner JC, Skidmore JW, Hill RJ, Griffiths DM. (1985). Erionite exposure and mesotheliomas in rats. Br J Cancer 51:727–30.

Webster I. (1970). The pathogenesis of asbestosis. In: Shapiro HA (ed.) Pneumoconiosis: Proceedings of the International Conference. Johannesburg, 1969. Cape Town: Oxford University Press, 117–9.

Woodworth CD, Mossman BT, Craighead JE. (1983). Induction of squamous metaplasia in organ cultures of hamster trachea by naturally occurring and synthetic fibers. Cancer Res 43: 4906–12.

Wright GW, Kuschner M. (1975). The influence of varying lengths of glass and asbestos fibres on tissue response in guinea pigs. Inhaled Part 4 Pt 2:455–74.

Yeager H, Jr., Russo DA, Yanez M, et al. (1983). Cytotoxicity of a short-fiber chrysotile asbestos for human alveolar macrophages: preliminary observations. Environ Res 30:224–32.