Asbestos: Yesterday's Insulator of Public Buildings, Today's Threat to Public Health

Florence Loi

H. Catherine W. Skinner, Advisor

Geoffrey Lowell Chupp, 2nd Reader

29 April 2013

A Senior Essay presented to the faculty of the Department of Geology and Geophysics, Yale University, in partial fulfillment of the Bachelor's Degree.

ABSTRACT

Malignant mesothelioma (MM), an aggressive cancer of the mesothelium, kills approximately 3,000 people annually in the United States, where over 20 million people are at risk of developing the disease. The average survival time of MM is only about a year because of its resistance to chemotherapy. 80% of MM in the Western World is associated with exposure to asbestos, a group of six fibrous minerals often used for insulation, including chrysotile, crocidolite, amosite, anthophyllite, tremolite, and actinolite. Crocidolite and amosite are the more potent forms but chrysotile is equally important because it makes up 95% of world asbestos production. Unfortunately, the mechanisms in which asbestos induces MM have not been well elucidated. The fibrous habit, length, and chemistry of asbestos minerals are believed to play a significant role but still need to be confirmed and detailed such that regulation can be more effective. MM induction may involve the activation of certain proteins such as HMGB-1, NF-κB and ERK1/2/5 and the inactivation of tumor suppression genes including CDK-inhibitors *p16*^{INK4A}*, p53*, *NF2*, and *p14ARF*. Studies are underway in developing therapies that intervene at these different levels. However, the discovery of these pathways is generally based on experiments with crocidolite only. Additional studies involving chrysotile are warranted because of its greater prevalence and because carbon nanotubes are structurally similar to chrysotile and its use of in biomedical applications is rising. Since asbestos exposure is associated with only 80% of MM, other factors have been proposed: radiation, erionite exposure, genetic predisposition, and SV40. Further research may result in safety measures such as limiting certain diagnostic scans or better treatment options.

1. MALIGNANT MESOTHELIOMA BACKGROUND

Mesothelial cells are specialized cells that line the thoracic, abdominal, and pericardial cavities and the outer surface of other internal organs (Dogan and Dogan, 2005). Malignant mesothelioma (MM) is a cancerous tumor of the mesothelium, the tissue formed by mesothelial cells (Dogan and Dogan, 2005). Pleural MM affects the mesothelial cellular tissues that line the lungs in the upper chest and peritoneal MM affects those that line and separate the breathing apparatus from the abdomen and other viscera (Dogan and Dogan,

2005). See Figures 1 and 2 for locations of the pleura and peritoneum. Pleural MMs are more common and are better defined pathologically than peritoneal MMs (Hillerdal, 1999).

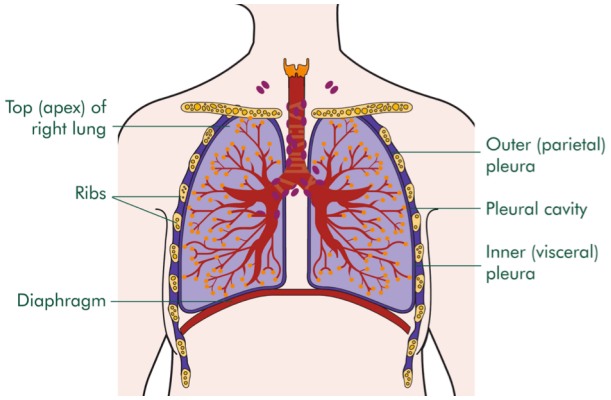

Figure 1. Structure of the lungs and pleura (Macmillian Cancer Support).

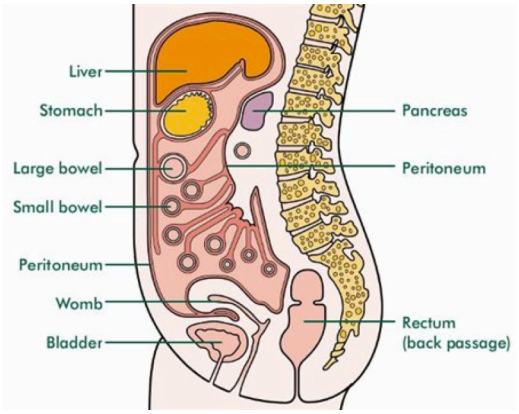

Figure 2. Structure of the abdomen. The peritoneum is shown as the thick line surrounding the abdominal organs (Macmillian Cancer Support).

Symptoms of pleural MM include dyspnea (shortness of breath), pain in the lower back and the side of the chest, persistent cough and hoarseness, difficulty in swallowing, unexplained weight loss, and excessive sweating (Dogan and Dogan, 2005). Symptoms of peritoneal MM also include unexplained weight loss as well as abdominal pain and swelling, nausea and vomiting, loss of appetite, and change in bowel movements (Dogan and Dogan, 2005). These symptoms certainly are not unique to MM so they are not helpful in its diagnosis but do serve as a warning sign for those with prior exposure to asbestos minerals (Dogan and Dogan, 2005).

MM in general can be difficult to diagnose, especially since some pathologists are not used to seeing this type of tumor (Carbone et al, 2012). The diagnosis usually starts with cytological analysis of pleural or peritoneal fluid (1/3 of all effusions are malignant; <1% of malignant effusions are caused by MM) (Carbone et al, 2012). In the standard process of diagnosis, MM is confirmed (in order) by a biopsy, immunohistochemistry, and if possible, electron microscopic study of the cellular tissues, which is the gold standard for diagnosis (Carbone et al, 2012). Electron microscopy is particularly important in distinguishing MM from adenocarcinomas because: 1) microvilli in MM tend to be abundant, long, slender, undulating, and often bifurcating whereas microvilli in adenocarcinomas tend to be sparse

and short, 2) tonofilaments are present in most MMs but rarely in adenocarcinomas, and 3) desmosomes occur more often in MM than adenocarcinomas (Fresco, 2005). Often, however, these procedures are not completed before a diagnosis is made (Carbone et al, 2012). Thus, MM is often confused with benign pleural lesions and metastatic pleural diseases (Hillerdal, 1983). Peritoneal MM, for example, is quite similar to peripheral carcinoma of the lung parenchyma: both can spread extensively on the pleura, usually cannot be resected, and respond poorly to chemotherapy and radiation therapy (Skinner et al, 1988). It may also resemble papillary carcinomas of the peritoneum and ovary (Husain et al, 2009). See Figure 3 for the location of the ovary. It is thought that the percentage of peritoneal MMs being misdiagnosed as carcinoma and vice versa is at least 20-25% (Carbone et al, 2012).

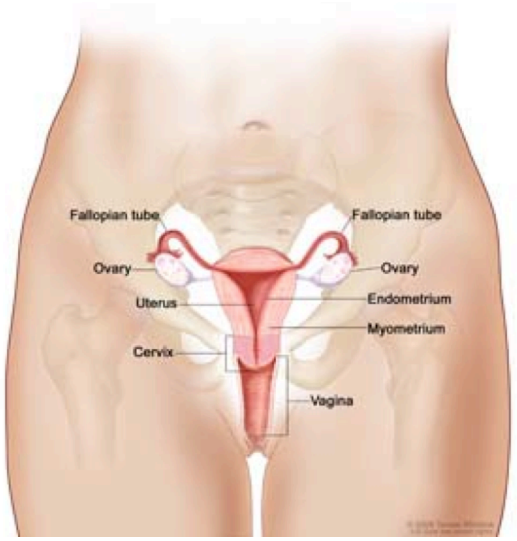

Figure 3. Anatomy of the female reproductive system, including the ovary (UofMHealth.org).

Second to lung cancer, MM has become the most significant occupational cancer affecting industrial workers worldwide since the last half of the twentieth century (Epidemiology of Mesothelioma, 2005). Nationwide, over 20 million people are at risk of developing MM as a result of asbestos exposure (Carbone et al, 2012). While nearly everyone who develop MM are expected to die from it within a few years (Carbone et al, 2012), the average survival time is less than twelve months after initial diagnosis due to MM's resistance to chemotherapy (Mossman et al, 1996). Thus, MM kills approximately 3,000 people each year in the United States alone (Ismail-khan et al, 2006). Clearly, the mechanisms of MM induction must be elucidated and exposure to risk factors must be eliminated in order to improve these statistics. Unfortunately, MM research has been slow because of limited funding (Carbone et al, 2012).

2. ASBESTOS BACKGROUND

Minerals are naturally occurring, crystalline inorganic elements or compounds with characteristic chemical compositions and crystal structures (Skinner et al, 1988). At least 394 minerals come in two forms: fibrous and non-fibrous. Fibers can be thought of as any small, elongate piece of matter regardless of its source or composition (Skinner et al, 1988). The term asbestos describes a family of six fibrous silicate minerals that have been mined and processed for industrial and commercial purposes (Skinner et al, 1988). These minerals come in both fibrous and non-fibrous forms but only the fibrous minerals are referred to as asbestos (See Figure 4) (Strohmeier et al, 2010).

Figure 4. Hand specimens of the six asbestos minerals and their non-fibrous counterparts (Strohmeier et al, 2010).

Asbestiform describes these asbestos minerals' special fibrous form: fine in thickness, flexible, separable, and arranged in a parallel fashion (Strohmeier et al, 2010). A significant difference between asbestiform fibers and their non-asbestiform counterparts is that crushing non-asbestiform minerals results in cleavage fragments whereas crushing asbestiform minerals results in finer fibers (Strohmeier et al, 2010). Cleavage, an inherent property of many minerals, is the tendency for a mineral species to fracture preferentially along certain planes of weakness based on its crystal structure (Strohmeier et al, 2010). Another characteristic of asbestiform fibers is their high aspect ratios (ratio of object's length to its thickness or width), which is typically greater than 20:1 (Strohmeier et al, 2010).

Approximately 80% of all MMs in the Western World are associated with asbestos exposure (Carbone et al, 2002). Over the past few decades, the most commonly mined of these six species has been chrysotile, which is mined mainly in Quebec and the Ural Mountains of Russia and comprises 95% of the world asbestos production (McDonald and McDonald, 2005; Epidemiology of Mesothelioma, 2005). Chrysotile is the sole asbestiform member of the serpentine mineral group while crocidolite, amosite, anthophyllite, tremolite, and actinolite are separate species in the amphibole mineral group (Strohmeier et al, 2010). These six minerals are composed of tetrahedral silicate ions $(SiO_4)^{4-}$, or four large oxygen ions (O^{2-}) surrounding a small silicon ion (Si^{4+}) (Skinner et al, 1988). The ideal composition of chrysotile is $Mg_6Si_4O_{10}(OH)_8$ and the general composition of amphibole minerals is $A_{0-1}B_2C_5T_8O_{22}(OH,F,Cl,O)_2$, where Na^+ and K^+ ions can enter the A site, Na^+, Li^+, Ca^{2+}, Mn^{2+}, Mg^{2+}, and Fe^{2+} can enter the B site, Mg^{2+}, Fe^{2+}, Mn^{2+}, Al^{3+}, Fe^{3+}, Cr^{3+}, and Ti^{4+} can enter the C site, and Si^{4+} and Al^{3+} can enter the T site (Skinner et al, 1988). See Table 1 for the ideal compositions for each of the asbestos minerals.

Table 1. The six regulated asbestos minerals. Chrysotile is the only member of the serpentine mineral group. The others are part of the amphibole mineral group (Ramos-Nino et al, 2005; adapted with information from Skinner et al, 1988).

Variety	Ideal Chemical Formula	Major Sources	Morphology
chrysotile	$Mg_6Si_4O_{10}(OH)_8$	US, Canada (Quebec), South Africa, Russia	curly, pliable
crocidolite	$Na_2(Fe^{2+},Mg)_3Fe^{3+}{}_2Si_8O_{22}(OH)_2$	South Africa, Western Australia	rodlike, durable
amosite	$(Fe^{2+},Mg)_7Si_8O_{22}(OH)_2$	South Africa (Transvaal Province)	rodlike, durable
anthophyllite	$(Mg,Fe^{2+})_7Si_8O_{22}(OH)_2$	Finland	rodlike, durable
tremolite	$Ca_2Mg_5Si_8O_{22}(OH)_2$	chrysotile deposits in Canada	rodlike, durable
actinolite	$Ca_2(Mg, Fe^{2+})_5Si_8O_{22}(OH)_2$	not mined	

A key difference between amphibole asbestos and chrysotile is that the former can contain significant amounts of iron. Additionally, while the amphiboles are rod-like, chrysotile has a unique structure (Ramos-Nino et al, 2005). Serpentine minerals are composed of virtually flat sheets of silica $(Si_2O_5)_n^{2n-}$ alternating with cationic sheets (ideally, $[Mg_3O_2(OH)_4]_n^{2n+}$) (Skinner et al, 1988). In chrysotile, these layers curl upon each other, forming concentric hollow cylinders (Skinner et al, 1988). See Figure 5 for a schematic diagram.

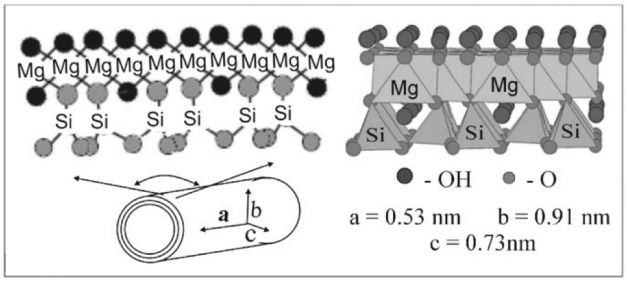

Figure 5. The schematic crystalline structure of chrysotile with the unit cell dimensions (Sprynskyy et al, 2011).

Asbestos as a name and its morphology are perhaps the most familiar inorganic fibers to the general public today due to their resistance to fire, decay, and electrical surges, flexibility, high tensile strength, and large surface area to mass ratio (Strohmeier et al, 2010). Asbestos containing products have been used in a number of industrial and commercial applications since antiquity (Skinner et al, 1988). By the late nineteenth century, asbestos coverings were found in engines for protection and in walls, ceilings, and around pipes in buildings as insulation and a fire retardant (Skinner et al, 1988). However, the incombustibility of asbestos does not come without its costs: since the first century

A.D., asbestos has been attributed to pulmonary disease in industrial workers (Skinner, Ross, et al, 1988). In fact, Pliny the Younger (A.D. 61-114) mentioned in a letter that slaves who worked with asbestos became sick (Skinner et al, 1988).

Asbestos is now widely accepted to have a causal association with asbestosis, pleural fibrosis, lung cancer, laryngeal cancer, and MM (Epidemiology of Mesothelioma, 2005; Carbone et al, 2002). According to the Los Angeles County Cancer Surveillance Program, New York State Cancer Registry, and 39 major Veterans Administration hospitals' registries, 169 out of 179 male MM patients (94%) and 14 out of 25 female MM patients (56%) have been significantly exposed to asbestos, especially those with pleural versus peritoneal MM (Spirtas et al, 1994). Still, the asbestos lung burdens were elevated in 14 out of 19 female MM patients (74%) who were not industrial workers, showing that non-occupational exposure to amosite, followed by tremolite and chrysotile, is a high risk factor as well (Roggli et al, 1997). Exposure to crocidolite and amosite, two members of the amphibole asbestos species, has been shown to be the most important contributing factor to MM (Ramos-Nino et al, 2005; Wagner et al, 1960a). For this reason, the World Health Organization has set its recommended permissible exposure limits for all asbestos fibers to less than 1.0F/cc (Dogan and Dogan, 2005).

3. PATHWAY OF ASBESTOS TO PLEURA

When inhaled, asbestos fibers of several micrometers in length and less than 5 can travel from the nose to the lungs via the bifurcating and shrinking bronchial tree (See Figure 6) (Skinner et al, 1988). The curled asbestos fiber, chrysotile, tends to be deposited in the upper airways, especially at bronchial or bronchiolar bifurcations (Harris and Timbrell, 1977). Regardless of morphology, most inhaled fibers stick to mucus lining the nose, throat, trachea, and bronchi and thus are cleared from the airways once the mucus is coughed up or swallowed (Dogan and Dogan, 2005). The rest end up in the lungs.

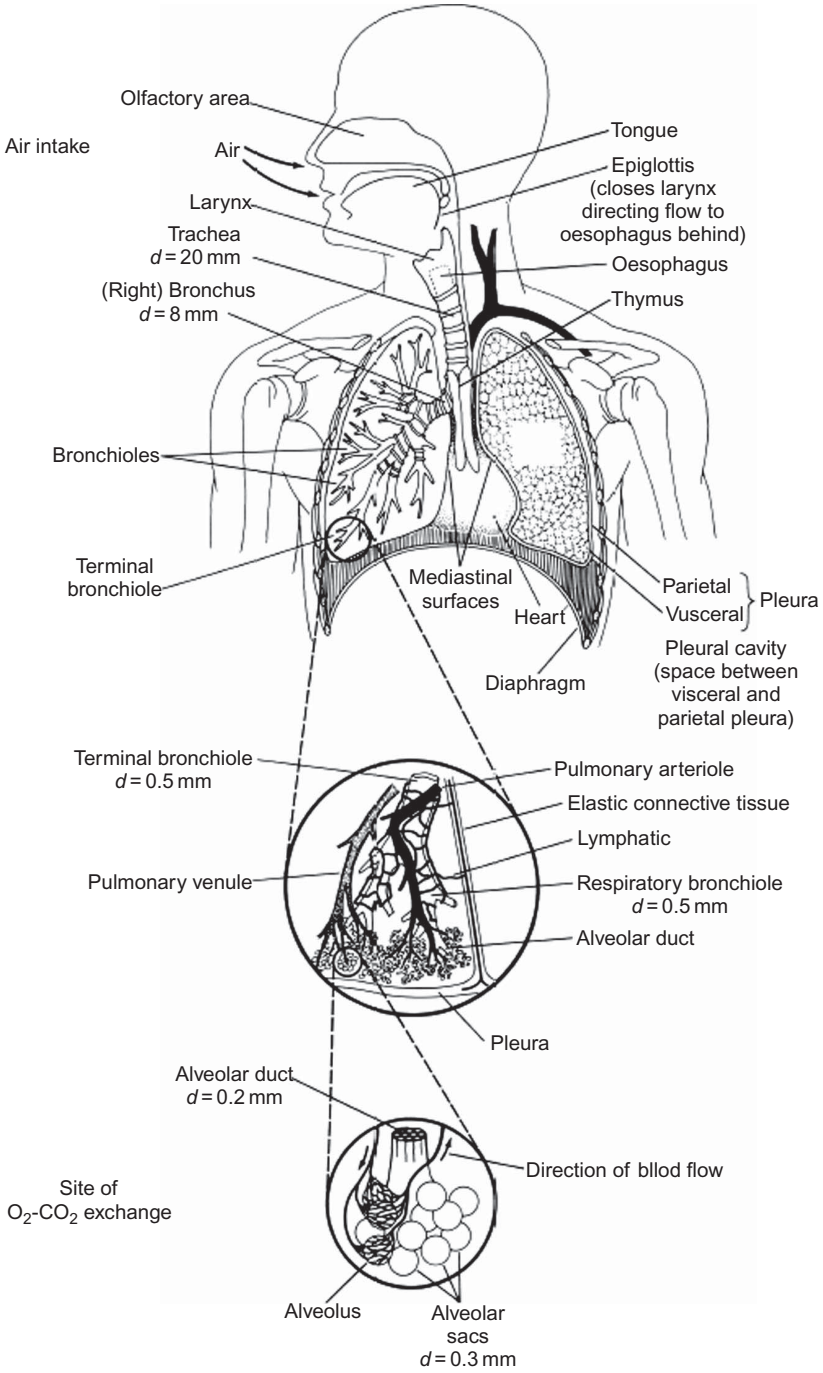

Figure 6. Schematic diagram of the human respiratory system. The gross anatomy of the lung, the covering membranes (pleura), airways and air sacs (alveoli) are shown. The average diameter of portions of the air flow system is indicated: trachea, 20 mm; bronchus, 8 mm; terminal and respiratory bronchioles, 0.5 mm; alveolar duct, 0.2 mm; alveolar sacs, 0.3 mm (Skinner et al, 1988).

From the lungs, there are two possible ways the fibers can reach the pleura: direct penetration of the lung tissues or via a lymphovascular route (Skinner et al, 1988). The high aspect ratio of the amphibole fibers results in a straight, needlelike morphology. It has

been hypothesized that this, along with the propulsive effects of the repetitive cyclic breathing, enables the fibers to penetrate through the lung into the tissues lining the pleura (Skinner et al, 1988). However, as mentioned before, chrysotile has a curly morphology so another pathway to the pleura must also exist: a lymphovascular route (Skinner et al, 1988). Thus, free fibers or those phagocytosed by macrophages can be cleared towards the pleura and lymphatics (Broaddus and Jaurand, 2002). Asbestos fibers larger than the diameters of macrophages cannot be engulfed and, thus, cannot get cleared (Blake et al, 1998) so those that end up in pleural tissues (excluding chrysotile) must have penetrated the lung. Smaller asbestos fibers, including chrysotile, follow the lymphovascular route. Asbestos fibers tend to accumulate in the pleural space, unable to pass through the draining lymphatic stomata, where fluids and proteins are usually removed (Broaddus and Jaurand, 2002).

4. LEVELS OF EXPOSURE AND MALIGNANT MESOTHELIOMA

Unlike lung cancer and asbestosis, neither a linear dose-response between asbestos exposure and MM or a clear threshold for MM induction seems to exist (Hillerdal, 1999; Carbone et al, 2002). Indeed, additional exposure above a certain threshold does not proportionally increase the risk of MM (Carbone et al, 2007) and there is even controversy surrounding that threshold (Goldberg, 2005). In other words, greater exposure does not necessarily mean higher risk of developing MM and a minimum exposure level has not been determined. However, this has been complicated by the fact that the amphibole forms of asbestos have a greater biopersistence than chrysotile so it is difficult to quantify exposure by looking at lung burdens (Carbone et al, 2002). However, it is known that long-term exposure to high concentrations of asbestos is a potent cause of lung diseases (Strohmeier, 2010). Other factors such as radiation, exposure to other mineral fibers, genetic risk, and exposure to viruses seem to play a role as well and will be discussed further later on.

5. GREATER POTENCY OF AMPHIBOLES THAN CHRYSOTILE

It has been well established that amphibole asbestos minerals play an important role in inducing MM (Wagner et al, 1960a; Spirtas et al, 1994). Although there is still an ongoing

debate over the role of the serpentine form in induction, evidence seems to favor the hypothesis that chrysotile does as well (Stayner et al, 1996; Wagner, 1997; Carbone et al, 2012). In the past, this was complicated by the fact that chrysotile veins typically contain amphibole asbestiform minerals such as tremolite and workers tend to be exposed to more than one form of asbestos (McDonald and McDonald, 1997; Carbone et al, 2012). For example, about 1% of Canadian chrysotile also contains tremolite (Carbone et al, 2002). In addition, MM cases in chrysotile-exposed workers generally occurred after more than 20 years of intense exposure (Wagner, 1997). However, many researchers in the field still propose that chrysotile is assumed to induce MM for the following reasons. 1) there have been cases of MM among non-contaminated chrysotile asbestos miners and millers (Cullen and Baloyi, 1991), 2) MM may not be solely induced by the tremolite in contaminated chrysotile because a mining town (Thetford, Quebec) with tremolite exposure levels 7.5 times greater than a similar mining town (Asbestos, Quebec) did not experience a higher incidence of MM after considering the different workforce sizes (Begin et al, 1992; McDonald et al, 1993), 3) the same is true when comparing Quebec miners and South Carolina textile workers (McDonald et al, 1980), 4) it is difficult to determine the amount of exposure to different asbestos minerals because of their differing biopersistences (chrysotile miners have more amphibole asbestos fibers than chrysotile fibers in their lungs) (Carbone et al, 2002) and 5) chrysotile makes up 95% of world asbestos production (Epidemiology of Mesothelioma, 2005) so it would be safer in terms of public health to assume it is carcinogenic.

It has been generally accepted that crocidolite is the most potent asbestos fiber in inducing MM, followed by amosite and then chrysotile (Hodgson and Darnton, 2000). In 1960, Wagner wrote the seminal paper definitively linking amphibole asbestos minerals to MM. His case studies support this varying potency hypothesis as the highest incidences of MM were near crocidolite mines relative to amosite and chrysotile mines (Wagner et al, 1960a). More recently, it has been estimated that the risk of MM for chrysotile workers is five times lower than that for mixed asbestos workers (Hughes and Weill, 1986).

It has been suggested that the greater potency of amphiboles is due to their greater biopersistence in the lung parenchyma (Churg, 1998), which is dependent on the minerals' different crystal-chemical composition (Ramos-Nino et al, 2005). Chrysotile breaks down and dissolves more rapidly so its half-life (weeks to months) is much shorter than the half-life for amphiboles (years to decades) (Churg, 1998). Indeed, the lung burden of amphibole asbestos fibers has been shown to increase with exposure whereas the lung burden of chrysotile does not (Albin et al, 1994). The longer a foreign substance persists in a biological system, the more opportunity it has to induce cell damage during regeneration of tissues and perhaps, chromosomal alterations and tumor growth (Dogan and Dogan, 2005). In fact, asbestos fibers tend to persist at tumor sites, acting as a stimulus for metaplasia, which is a pathological process where normal epithelium is converted into rapidly proliferating squamous epithelium (Woodworth et al, 1983). Crocidolite and amosite have been shown to be stronger metaplasia stimuli than chrysotile (Woodworth et al, 1983). This is consistent with the finding that patients with chrysotile-induced MM tend to have several hundred-fold larger lung fiber burdens than patients with crocidolite- or amosite-induced MM (Churg, 1988), meaning more chrysotile fibers need to be present to induce metaplasia to have a similar effect as amphibole asbestos fibers. Thus, even though chrysotile makes up 95% of the world asbestos production (Epidemiology of Mesothelioma, 2005), the number of chrysotile-induced MM cases is relatively small compared to amphibole-induced MM cases and the minimum required chrysotile exposure for MM induction is greater than the minimum required amphibole exposure (Churg, 1988). Rat lung inhalation studies also support the hypothesis that biopersistence is an important indicator for the potential pathogenicity of fibers (Hesterberg et al, 1998). Biopersistence is important to MM induction because the latency period tends to be long.

6. MALIGNANT MESOTHELIOMA LATENCY

The latency period of MM is the time that elapses between the first asbestos exposure to the diagnosis of the cancer. For those who develop MM, it generally takes 20-40 years (Berman and Crump, 2003). However, it can take up to 71 years (Bianchi et al, 2007). The lowest recorded latency period is 10 years but only about 1% of all MM cases have latency periods less than 15 years (Lanphear and Buncher, 1992).

The wide range of latency periods may be due to the intensity of exposure but this is still debated. A survey of pleural MM cases in Northeastern Italy suggests that industrial workers with shorter latencies experienced higher levels of asbestos whereas those with longer latencies experienced lower levels of asbestos (Bianchi et al, 2007).

The long latency period may explain why the incidence of pleural disease is still on the rise despite decreases in occupational exposure to asbestos fibers and lung disease (Goldberg, 2005). Unfortunately, mortality rates due to MM in most industrial countries is expected to continue rising by 5-10% each year for the next few decades (Goldberg et al, 2006). Still, for males living in the United States, the maximum risk occurs for those born between 1925 and 1929 (Harris and Kahwa, 2003) and the incidence of MM has been steady since 1994 (Carbone et al, 2012), suggesting that the decreases in asbestos exposure have indeed been effective.

It is important to note that despite long latency periods, MM actually is a rapidly growing aggressive cancer resulting in clinical symptoms in a matter of years, rather than decades (Carbone et al, 2012). This implies that a long period of time is necessary for asbestos to induce MM, further implying that the window of opportunity to arrest or delay carcinogenesis is long (Carbone et al, 2012).

7. MECHANISMS OF MALIGNANT MESOTHELIOMA INDUCTION BY ASBESTOS

The long latency of MM suggests that multiple genetic alterations are necessary for tumorigenic conversion (i.e., the conversion of normal mesothelial cells into malignant ones) (Molecular Biology, 2005). This multistep carcinogenesis hypothesis is supported by the early recognition of recurrent chromosomal abnormalities (Molecular Biology, 2005).

7.1 Asbestos Characteristics: Fibrous Habit, Length, and Surface Activity

Certainly, mechanisms for pulmonary disease induction must start with the fibrous morphology of asbestos because inorganic material have been observed in the lymph nodes, spleen, and sputum of people afflicted with asbestosis (Stewart et al, 1931). This means that inhaled asbestos fibers must travel from the pulmonary cavity to different sites throughout the body. Although any particle greater than 5 μm in length typically do not

make it to the distal respiratory airways, those with a needle-like shape that do can certainly migrate to and accumulate in the pleura via tissue planes and lymphatic channels (Stanton et al, 1981). Once in the body, the fibrous habit of asbestos can induce disease. Indeed, experimental studies on rats, hamsters, and mice have shown that intrapleural injections of fibers such as amphibole asbestos, chrysotile, erionite, refractory ceramic fibers, glass wool, glass filaments, rock wool, and slag wool can all induce pleural MM (Stanton et al, 1981; Saffinotti, 2005). Fibers in animal models have been demonstrated to 1) induce epithelial cells and macrophages to release certain inflammatory mediators, cytokines, and growth factors by epithelial cells and macrophages, which may alter epithelial and mesothelial cell proliferation, 2) activate certain cells by binding to their plasma membranes, and 3) induce many intracellular signaling pathways and transcription factors (Saffinotti, 2005). The needle-like morphology of fibers can also repeatedly cause cell tissue injury, which may be followed by proliferation and genetic damage that give rise to an autonomously proliferating tumor (Antoniades, 1992). The importance of a fibrous habit to its toxicity is highlighted by the observation that riebeckite, the non-fibrous crocidolite counterpart with the same chemical composition, is generally nontoxic (Broaddus and Jaurand, 2002).

Fiber length is another factor worth considering in MM induction. *In vivo* and *in vitro* studies demonstrate that compared to long-length fibers (>5μm, especially >8-10μm in length), short-length fibers have relatively little carcinogenic activity, including induction of chromosomal abnormalities and transformation (Report of the expert panel on health effects of asbestos and synthetic vitreous fibers, 2003; Broaddus and Jaurand, 2002). In fact, inhaled fibers greater than 20μm in length are far more potent than fibers less than 10μm in inducing pulmonary tumors (Davis et al, 1986). Even grinding fibers to shorter shapes decreases their toxicity (Broaddus and Jaurand, 2002). Intraperitoneal injection of long amosite fibers, but not short amosite fibers, resulted in an exaggerated inflammatory response (Donaldson et al, 1989). One possible reason longer fibers are more carcinogenic is that particles longer than 5μm that make it to the distal respiratory airways can typically avoid macrophage clearance due to their long length (Stanton et al, 1981; Skinner et al, 1988). Still, they are much less likely than shorter fibers to reach the pleura (Carbone et al,

2012). However, the amphibole asbestos fibers of most concern in terms of health risk are those longer than 10μm with diameters less than 0.4μm (Berman and Crump, 2003).

The surface of asbestos fibers has been shown to absorb proteins (Desai and Richards, 1978), phospholipids (Jaurand et al, 1983) and DNA (Gan et al, 1993). This adsorptive property affects the fibers' abilities to interact with cell surfaces, may capture chemical carcinogenic molecules, and may provide a site for chemical reactions (Broaddus and Jaurand, 2002).

7.2 DNA Alterations

MM is a tumor of mesothelial cells so asbestos must target these cells to induce a genetic change that leads to malignant transformation. Results from animal models and human mesothelial studies suggest that both serpentine and amphibole forms of asbestos can alter the DNA of mesothelial cells, thereby inducing cancer. Karyotypic analyses of human MMs suggest that the chromosomes 1, 2, 3, 6, 9, 11, 17, and 22 are typically the ones affected numerically or structurally (Gibas et al, 1986); the most common changes are deletions, inversions, or translocations of chromosome 3 (Popescu et al, 1988), suggesting the presence of a particularly important gene on this chromosome. Because they can be phagocytosed by mesothelial cells (Jaurand et al, 1979), asbestos fibers can directly alter DNA by mechanically preventing chromosomes from segregating properly during mitosis (Olofsson and Mark, 1989). Asbestos can also alter the DNA of mesothelial cell indirectly by causing mesothelial cells and macrophages to release cytokines, such as high-mobility group box 1 protein (HMGB-1) (Carbone et al, 2012) and extracellular signal regulated kinases (ERKs) (Shukla et al, 2013), and to create oxidative stress through the generation of mutagenic reactive oxygen (ROS) and nitrogen (NOS) species (Ramos-Nino et al, 2005).

7.2.1 Release of HMGB-1 And Activation of NF-κB

Any particle deposition in the respiratory tract can induce an inflammatory response (Skinner et al, 1988). Repeated deposition leads to chronic inflammation (Skinner et al, 1988). Evidence suggests that asbestos-induced inflammation is linked to asbestos carcinogenesis (Yang et al, 2010). Recent findings indicate that crocidolite asbestos induces necrotic cell death of primary human mesothelial cells, releasing high-mobility group box 1

proteins (HMGB-1), which both starts and promotes inflammation (see Figure 7) (Yang et al, 2010). HMGB-1 does this by inducing macrophages to secrete tumor necrosis factor-alpha (TNF-α), which then activates the nuclear factor kappa B (NF-κB) pathway and initiates a chronic inflammatory response (Yang et al, 2010). Macrophages can actively release additional HMGB-1, further promoting chronic inflammation (Bonaldi et al, 2003). NF-κB, up-regulated in MM cells (Sartore-Bianchi et al, 2007), promotes cell survival via proliferation, apoptosis, and chemokine/cytokine production (Heintz et al, 2010) and, paradoxically, the overexpression of antioxidant enzymes such as manganese superoxide dismutase (Kinnula, 1999). This enzyme, indeed overexpressed in human MM, can make mesothelial cells with asbestos-induced DNA damage more resistant to oxidative stress than normal mesothelial cells and prevents further cell injury (Kinnula, 1999). This means that once some mesothelial cells undergo asbestos-induced necrotic death, other damaged mesothelial cells are protected from it, allowing MM to eventually develop as the genetic damage propagates (Carbone et al, 2012). The significance of this pathway in MM induction is supported by the observation that asbestos does not induce pulmonary fibrosis in transgenic mice without TNF-α receptors (Liu et al, 1998). On a side note, asbestos can also induce apoptosis in 8-18% of mesothelial cells (Broaddus et al, 1996), providing a possible protective mechanism against MM development by inducing cell death without the release of HMGB-1. Chemopreventative approaches that inhibit a chronic inflammatory response to asbestos (especially by blocking HMGB-1) are being tested on animal models to decrease the risk of MM in those already exposed to asbestos (Carbone et al, 2012).

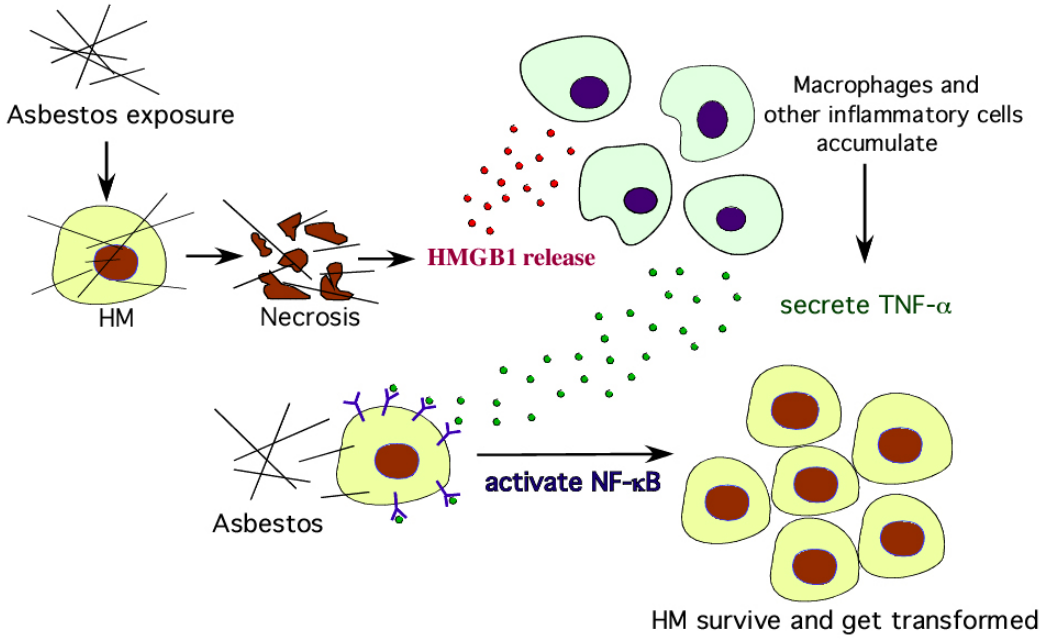

Figure 7. After asbestos induces necrosis of HM (human mesothelial cells), HMGB-1 is released into the extracellular space. HMGB-1 induces an inflammatory response in which macrophages and other inflammatory cells accumulate and TNF-α is secreted. TNF-α activates the NF-κB pathway, allowing HM to survive after asbestos exposure. Thus, HM with asbestos-induced DNA alterations continue to divide rather than die, eventually developing into MM if key genetic damage takes place (Carbone et al, 2012).

7.2.2 Activation of ERK Pathways

The epidermal growth receptor (EGFR), overexpressed in MM (Destro et al, 2006), is required for proliferation of mesothelial cells (Ramos-Nino et al, 2005), partially by regulating NF-κB (Molecular Biology, 2006). It also plays an important role in cell survival, motility, attachment, and transformation (Heintz et al, 2010). Unlike their non-fibrous counterparts riebeckite and antigorite, crocidolite and chrysotile have been demonstrated to activate EGFR in mesothelial cells, leading to the activation of several downstream ERKs (Zanella et al, 1996). These ERKs include ERK1, ERK2, and ERK5 (Ramos-Nino et al, 2005; Kroczynska et al, 2006; Shukla et al, 2013).

ERK5 can be activated by crocidolite through a c-met pathway in addition to through EGFR (Shukla et al, 2013). Silencing studies have demonstrated that ERK5 regulates a wide variety of transcription factors such that proliferation of mesothelial cells and inflammation increases and apoptosis decreases (see Figure 8) (Shukla et al, 2013). Proliferation/survival related genes and transcription factors that ERK5 regulates include

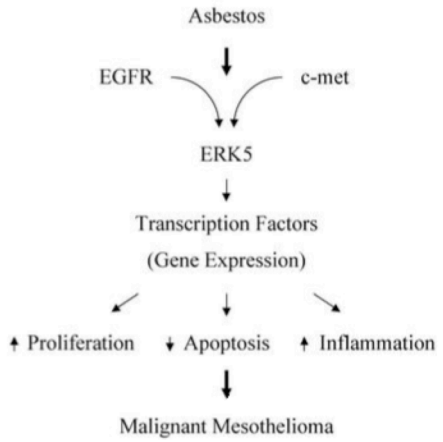

Figure 8. Schematic diagram of how ERK5 can lead to MM development (Shukla et al, 2013).

p21 activated kinase 7 (PAK7), chemokine ligand 5 (CCL5), and AKT 3 (Shukla et al, 2013). ERK5 also regulates invasion/migration related genes, which aid in proliferation, including CCL5, matrix metalloproteinases 1 and 9 (MMP1 and 9) and ATP binding cassettes (ABC) such as (ABCC2, ABCA8, ABCC5, and ABCB) (Shukla et al, 2013). ERK5 increases the levels of pro-inflammatory molecules such as interleukin (IL-8), vascular endothelial growth factor (VEGF), macrophage chemoattractant protein-1 (MCP-1), and CCL5 (Skula et al, 2013). IL-8, VEGF, and CCL5 are cytokines involved in angiogenesis and are known to be elevated in MM (Skula et al, 2013). MCP-1 and CCL5 play important roles in the chemoattraction of different inflammatory cells (Shukla et al, 2013). Because of the anti-proliferatory, anti-inflammatory, proapoptotic, and antiangiogenic properties associated with ERK5 silencing, ERK5 inhibitors have been suggested for MM treatment (Shukla et al, 2013).

Another study shows that crocidolite may act through ERK1 and ERK2 to induce MM by stimulating cell division (Ramos-Nino et al, 2005) and promoting cell invasion (Kroczynska et al, 2006). Crocidolite-induced phosphorylation of ERK1 and ERK2 leads to the activation of the transcription factor activator protein-1, AP-1, which stimulates cell division (Ramos-Nino et al, 2005). Similar to ERK5, the activation of this ERK1/ERK2 pathway also induces and releases MMP-1 and MMP-9, promoting cell invasion (Kroczynska et al, 2006). Crocidolite-related upregulation of EGFR mRNA and proteins in mesothelial cells (Zanella et al, 1999) has been suggested to play a key role in the induction of MMPs (Shukla et al, 2006).

7.2.3 Generation of ROS and NOS

One way the lung protects itself from foreign materials is through the sequestration of these objects by coating them with proteins that may contain significant amounts of iron (Skinner et al, 1988). These “ferruginous bodies” can be detected with the electron and,

sometimes, with the light microscope (Skinner et al, 1988). Iron found in and/or on asbestos fibers may induce MM by promoting oxidative stress through the macrophage generation of ROS (Hansen and Mossman, 1987) and RNS, as shown by studies on animal models and cell cultures (Ramos-Nino et al, 2005). Indeed, the high iron content of crocidolite and amosite appear to play a significant role in the generation of ROS, which includes the highly DNA-damaging hydroxyl radical (OH^-) (Heintz et al, 2010). In cell-free solutions and in alveolar and peritoneal macrophages, inhalation and *in vitro* phagocytosis of asbestos fibers resulted in the release of H_2O_2, the superoxide radial (O_2^-), and RNS (Heintz et al, 2010). ROS and RNS are also regulated by the previously discussed NF-κB (Molecular Biology, 2006). Together, ROS and RNS can oxidize and/or nitroslylate ferrous heme to ferric heme, thereby damaging certain proteins crucial to normal mesothelial cell structure and function (Ramos-Nino et al, 2005; Kinnula, 1999). In a dose-response fashion, ROS and RNS may initiate cell signaling pathways both inside and outside of mesothelial cells to induce cell proliferation and injury (Heintz et al, 2010). The pathogenetic activity of ROS can be enhanced by membrane damage, inducing the release of inflammatory compounds, which leads to fibrosis and breaks in DNA strands (Dogan and Dogan, 2005).

The greater potency of amphibole asbestos fibers versus chrysotile fibers may lie in the relatively iron rich amphibole composition (see Table 1). Crocidolite is especially rich in iron, containing up to 36% iron by weight (Ramos-Nino et al, 2005). Again, fiber length is important because asbestos fibers longer than 10 μm, particularly amphibole asbestos minerals, tend to have a coat of iron-rich proteins, including ferritin and hemosiderin, further promoting the production of mutagenic ROS (Hansen and Mossman, 1987; also reviewed in Heintz et al, 2010).

7.3 Inactivation of Tumor Suppressor Genes

Tumor suppressor gene protein products downregulate cell proliferation and upregulate apoptosis (Molecular Biology, 2006). Currently, three tumor suppressor genes are confirmed to play a pathogenetic role in MM: CDK-inhibitors *p16*^{INK4A}*, p53*, and *NF2* (Molecular Biology, 2006). p14ARF mutation/loss is another common acquired genetic

lesion in MM (Carbone et al, 2002). However, the mechanisms through which asbestos inactivates these genes has yet to be elucidated (Molecular Biology, 2006).

7.4 Unique susceptibility of Mesothelial Cells

One last thing to consider is the structure of mesothelial cells. A study shows that to kill cultured human mesothelial cells, crocidolite, amosite, and chrysotile require exposure levels of at least 50 fold less than those necessary to kill cultured human lung fibroblasts (Gabrielson et al, 1992). This suggests that mesothelial cells are sensitive to asbestiform minerals.

8. NON-ASBESTOS ASSOCIATIONS OF MALIGNANT MESOTHELIOMA

MM is often but not always associated with asbestos exposure: most pleural MMs in men are associated with asbestos compared to 30% of pleural MMs in women, 30% of peritoneal MMs in men and nearly nonexistent for pleural MMs in women (Carbone et al, 2012). Overall, only 80% of all MM in the Western World is associated with asbestos exposure (Carbone et al, 2002). Furthermore, MM also occurs in children (Fraire et al, 1988) and since, as previously discussed, asbestos-induced MM has a latency period on the order of decades, these cases suggest a non-asbestos etiology (Hillerdal, 1999). While it is important to note that it is possible for asbestos to penetrate through the placenta, as demonstrated by the presence of asbestos fibers in the lungs of stillborn infants (Haque et al, 1996), not all of these childhood MM cases were associated with known asbestos exposures (Hillerdal, 1999). Examples of these other factors include exposure to radiation, erionite (a non-asbestos, fibrous zeolite mineral), genetics and simian virus 40 (SV40). It is interesting to note that smoking does not increase the risk of MM, unlike in the cases of lung cancer and asbestosis (Carbon et al, 2002).

8.1 Radiation

Exposure to ionizing radiation such as Thorotrast, a diagnostic radiographic contrast medium that cannot be excreted and decays in the body, has been suggested to induce MM (Hillerdal, 1999; Epidemiology of Mesothelioma, 2005; Goodman, 2009). Initially, no significant association between radiation and MM was found in a large retrospective study of women with breast cancer and patients with Hodgkin's disease who were treated with

radiotherapy (Neugut et al, 1997; Epidemiology of Mesothelioma, 2005). However, a later review of many epidemiology studies revealed statistically significant increases in the risk for MM development due to Thorotrast and radiation therapy; nuclear power plant workers show some statistically significant associations as well, though at a lower rate (Goodman et al, 2009). Furthermore, some of the previously mentioned ferruginous coatings on longer asbestos fibers have also been found to contain high concentrations of radium, adding another source of ionizing radiation (Nakamura et al, 2009). Studies investigating the effect of radon on the risk of mesothelioma are limited. However, one study shows that while radon alone does not induce MM in 60 rats, it did have synergistic effects on bronchopulmonary carcinomas (Moncaux et al, 1994). Radon has been shown to cause lung cancer in humans but its role in MM induction is still inconclusive (Boffetta, 2006). While radiation does not definitively cause MM, the association is strong (Goodman et al, 2009).

8.2 Erionite

In the 1970s, a MM epidemic was unexpectedly discovered in an area of no known asbestos deposits, manufacture, or use: in the small villages of Karain, Sarihidir, and Tuzkoy in the Cappadocian region of Turkey, where inhabitants live in houses built with stones containing high levels of erionite (Baris et al, 1992; Roushdy-Hammady et al 2001). Erionite, a fibrous zeolite that is naturally occurring, is technically not asbestos by the United States EPA definition (US Code of Federal Regulations, 2003). It is not even linked to lung cancer, unlike asbestos (Carbone et al, 2012). However, its dimensions and properties are most similar to amphibole asbestos varieties (Epidemiology of Mesothelioma, 2005). Fibrous erionite may actually be much more potent than asbestos in inducing MM: 40 out of 40 rats (100%) injected with erionite from Oregon developed MM versus only 19 out of 40 rats (48%) injected with chrysotile, 2 out of 40 rats (5%) injected with the non-fibrous form of the zeolite, and 1 out of 40 rats (2.5%) injected with saline as a control (all intrapleurally injected) (Wagner et al, 1985). It has even been suggested that erionite is the most potent natural mineral carcinogen (Dogan, 2005). The high incidence of MM is unprecedented and only sporadic cases of erionite-induced MMs have been recorded

outside of Turkey (Ilgren et al, 2008; Kliment et al, 2009), suggesting genetics may play a significant role in MM induction (Carbone et al, 2012).

8.3 Genetics

Genetics may also play a role in MM carcinogenesis in these Turkish villages. In Tuzkoy, some families experienced a higher incidence of MM than others despite the fact that all villagers essentially were exposed to similar amounts of erionite dust (Dogan, 2005). A six-generation pedigree analysis of 526 relatives living in Karain and Tuzkoy suggests that the genetic transmittance does indeed exist and it exists in an autosomal dominant way (Roushdy-Hammady et al, 2001). Furthermore, other studies show that not all those are exposed to high levels of asbestos fibers develop MM (Carbone et al, 2002; Wagner et al, 1960b) while others develop it after only limited exposures (Carbone et al, 2002; Roushdy-Hammady et al, 2001). Currently, several research scientists, such as M Carbone, N Cox (University of Chicago), and JR Testa (Fox Chase Cancer Center), are attempting to identify the gene(s) leading to susceptibility to mineral fiber carcinogenesis in hopes of devising specific mechanistic therapies (Carbone et al, 2012).

8.4 SV40

Simian virus 40 (SV40), a DNA tumor virus endemic to the Asian macaque species of monkeys, has been suggested as a co-carcinogen with asbestos in human MM induction (Carbone et al, 2012). Millions of people worldwide have been exposed to SV40 through contaminated 1954-1978 poliomyelitis vaccines (Epidemiology of 2005; Cutrone et al, 2005). SV40 DNA has been detected in a number of human MM cases, but there is no general consensus on its prevalence. One paper stated that 29 of 48 analyzed human MM biopsies (60%) revealed the presence of SV40 sequences (Carbone et al, 1994). However, numbers can range from 5-6% (Ziegler et al, 2007) to up to 60% (Epidemiology of Mesothelioma, 2005) to 52-90% (Jasani et al, 2001).

The seminal paper on virus-induced MM in mammals involved intrapleurally injecting SV40 into 11 hamsters, all of which developed MM (Cicala et al, 1993). Later, results from human MM biopsies demonstrate that SV40 binds and inactivates cellular p53 and retinoblastoma (Rb)-family proteins, which are tumor suppressor proteins (Carbone et al,

2003; Bocchetta et al, 2008). Tag, the large tumor antigen of SV40, binds and inhibits several tumor-suppressor genes such as p53 and pRb (Carbone et al, 2002). Tag-p53 complexes specifically activate the IGF-I signaling pathway, promoting malignant cell growth (Bocchetta et al, 2008). They likely antagonize p53-induced apoptosis as well (Molecular Biology, 2006). Together, the expression of SV40 Tag only in MM cells (none in nearby stromal cells) and the *in vitro* arrest of MM cell growth after antisense T-antigen treatment indicate that SV40 contributes to tumor development (Carbone et al, 2002). This tumor development may lead to MM because human mesothelial cells have been found to be particularly susceptible to SV40 infection (Bocchetta et al, 2000). The synergistic effects of crocidolite and SV40 have been demonstrated in both hamster and human mesothelial cell experiments. In hamsters infected with SV40 and both intrapleurally and intraperitoneally injected with crocidolite, SV40 alone did not cause MM in 28 hamsters, crocidolite alone caused MM in 6 of 29 hamsters (20%), and SV40 and asbestos together caused MM in 27 of 30 hamsters (90%) (Kroczynska et al, 2006). In human mesothelial cells, exposure to both crocidolite and SV40 leads to higher rates of malignant cell transformation than with exposure to SV40 alone (Bocchetta et al, 2000). Still, a retrospective study by the Institute of Medicine has found no conclusive epidemiological evidence supporting or disputing the hypothesis that SV40-contaminated vaccines played a role in human MM development (Stratton et al, 2003).

If SV40 can be a cofactor, can common viruses such as rhinovirus, cytomegalovirus, HIV, hepatitis C, or influenza increase the risk of MM as well? The number of studies in the literature is limited. There have been at least two reported cases of HIV-positive patients with no known exposures to asbestos who died of MM (Behling et al, 1993; Kordossis et al, 1994). Of these two cases, it is possible that one could be due to cytomegalovirus instead (Behling et al, 1993). Thus, there is no compelling evidence to suggest these viruses and their effect on MM risk deem further investigation yet.

9. CARBON NANOTUBES

Again, a fibrous habit has been demonstrated to be essential in MM induction. Carbon nanomaterials have multiple applications including in industrial and medical fields;

however, possible harmful health effects of certain types of carbon nanomaterials are of great concern (Palomaki et al, 2011). In fact, the very unique characteristics of nanomaterials (e.g., ability to bind and deliver other molecules to target objects, high surface area and reactivity) that make them ideal for certain applications may be for very same properties that lead to negative health effects (Kagan et al, 2005**;** Fadeel et al, 2007). One type, the carbon nanotube (CNT), consists of a sheet welded into a tube (Palomaki et al, 2011), similar to the curled fibrous morphology of chrysotile. If this unique morphology of chrysotile is responsible for the induction of MM, then perhaps prolonged exposure to CNT can induce MM as well. Several *in vitro* studies have shown that single-walled carbon nanotubes (SWCNT) generally avoid being phagocytosed by alveolar macrophages whereas SWCNT modified chemically or by adsorbing macromolecules (e.g. the protein albumin, the phospholipid phosphatidylserine) are more readily engulfed by several phagocytic cells such as human macrophages and dendritic cells (reviewed in Shvedova et al, 2009). However, a 2008 study by Takagi et al found that like crocidolite, pristine multi-wall carbon nanotubes (MWCNT) induces MM in p53 heterozygous mice when intraperitoneally injected. The mortality rate for the MWCNT-exposed mice was greater than that for the asbestos-exposed mice (Takagi et al, 2008). Although this study was criticized for using an unusually high exposure dose (3 mg/mouse), its purpose was to determine whether MWCNT could induce MM, not which exposure dose is required for its induction. Another study shows that only intraperitoneal injection of long MWCNT in mice (as opposed to short MWCNT) results in pathogenic behavior qualitatively and quantitatively similar to asbestos exposure such as inflammation and formation of certain lesions called granulomas (Poland et al, 2008). *In vitro* MWCNT exposure of human mesothelial cells has resulted in DNA damage and activation of AP-1 and NF-κB (Pacurari et al, 2008). Although, there is no current *in vivo* evidence that CNT can induce human MM due to its long latency period (Shvedova et al, 2009), a recent study indicated that like asbestos fibers, CNT clearance from the lungs is impaired (Donaldson et al, 2011) and long CNT can reach the subpleural tissues in mice after inhalation (Ryman-Rasmussen et al, 2009). However, these cautionary results and the poor prognosis of MM highlight the need for further research before introducing carbon nanotubes into the market in order to prevent MM as well as other diseases.

10. MINIMIZING EXPOSURE TO ASBESTOS IN THE UNITED STATES

There is no general asbestos ban in the United States, though many applications are regulated by the Toxic Substances Control Act (EPA). In 2012 Carbone et al identified a few oversights: 1) certain commercial products are still allowed to contain asbestos, 2) outcrops containing asbestos and erionite have not been identified so people do not know which areas to avoid (Maher, 2010), and 3) various non-asbestos minerals mined for commercial applications may unknowingly contain asbestos (e.g., some deposits of vermiculite and talc). However, when products containing asbestos (e.g., building materials, roofs, brakes) degrade, asbestos fibers are released into the environment, increasing non-industrial exposures. Usually, encapsulation is better than removal, especially when the asbestos is well contained (Hillerdal, 1999).

11. CONCLUSION

The mechanisms in which the six regulated forms of asbestos – chrysotile, crocidolite, amosite, anthophyllite, tremolite, and actinolite – induce MM remain to be elucidated. In terms of the asbestos fibers, the carcinogenic characteristics need to be determined, whether it is the asbestiform habit, fiber length, mineral chemistry, or any combination of the above. If the fibrous habit alone plays a major role, structurally similar synthetic substitutes may pose a significant risk of MM development as well. With the rise of nanomaterials especially in biomedical applications, the role of chrysotile in MM induction particularly needs to be clarified since chrysotile and CNT share similar structures. The specific dimensions of fibers that can induce MM need to be determined because currently, OSHA only regulates fibers longer than 5 μm and have an aspect ratio of 3:1 (Occupational Safety and Health Administration). Regulation may need to be stricter and the varying carcinogenicity of different mineral species should be considered as well.

In terms of the biology side of MM induction, the underlying cause of mesothelial cell sensitivity to asbestos-induced MM needs to be better understood so that therapies can be developed to prevent MM. Currently, the release and/or activation of certain proteins, including HMGB-1, NF-κB and ERK1/2/5, are known to play a significant role in MM induction. The genesis of ROS and RNS enhance the pathogenic activity of these activated

pathways. Somehow, important tumor suppression genes associated with MM such as CDK-inhibitors *p16*^{INK4A}, *p53*, *NF2*, and *p14ARF* are inactivated. The good news is that therapies are being developed to inhibit some of these mentioned pathways, which is expected to be effective because their activation starts early and the latency period of MM is long. However, the studies that elucidated these pathways were based on crocidolite only. Chrysotile should be studied further since it is more prevalent than crocidolite.

Since asbestos exposure is associated with only 80% of MM, other factors that put people at risk of developing MM need to be determined. Proposed risk factors include radiation, erionite exposure, genetic predisposition, and SV40. If these can be confirmed, safety measures such as limiting certain diagnostic scans or gene therapies can be implemented to prevent MM development.

Lastly, the elucidation of asbestos-induced MM can lead to better treatment options since chemotherapy is currently ineffective and the average survival time is only one year. All of these measures should be considered in order to better prevent and treat MM.

ACKNOWLEDGEMENTS

I would like to thank my advisor Catherine Skinner, Senior Research Scientist and Lecturer in the Yale Departments of Geology & Geophysics and Orthopaedics & Rehabilitation, for introducing me to the topic of minerals and human health. I am extremely grateful for her guidance in narrowing down and developing a research topic, her expertise on asbestos, and her enthusiastic and encouraging mentorship throughout the process. I would also like to thank Dr. Geoffrey Chupp, Associate Professor of Medicine and Director of the Yale Center for Asthma and Airways Disease and of the Pulmonary Function Laboratory at Yale-New Haven Hospital, for being my second reader and providing expertise on pulmonary disease. Additional thanks go to the Director of Undergraduate Studies, Dave Evans, for all the opportunities he provided me with, including collecting rock samples in Bahia, Brazil with Finnish postdoctoral associate, Johanna Salminen and participating in a geology study abroad program in Christchurch, New Zealand. Finally, I would like to thank the rest of the Geology and Geophysics Department for making the major an enjoyable one.

REFERENCES

Albin, M., F.D. Pooley, U. Stromberg, R. Attewell, R. Mitha, L. Johansson, and H. Welinder. 1994. Retention patterns of asbestos fibres in lung tissue among asbestos cement workers. Occupational and Environmental Medicine 51:205-211.

Antoniades, H.N. 1992. Linking cellular injury to gene expression and human proliferative disorders: examples with the PDGF genes. Molecular Carcinogenesis, 6:175-180.

Baris Y.I, L. Simonato, R. Saraci, and R. Winkelmann. 1992. The epidemic of respiratory cancer associated with erionite fibers in the Cappadocian region of Turkey. In Elliott, P., J. Cuzick, and D. English, eds., *Geographical and Environmental Epidemiology: Methods for Small-Area Studies*. Oxford University Press, Oxford, England. 310-322 pp.

Begin, R., J. Gauthier, M. Desmeules, and G. Ostiguy. 1992. Work-related mesothelioma in Quebec, 1967-1990. American Journal of Industrial Medicine 22:531-542.

Behling, C.A., P.L. Wolf, and P. Haghighi. 1993. AIDS and malignant mesothelioma—is there a connection? Chest 103(4):1268-1269.

Berman, D.W. and K.S. Crump. Final draft: technical support document for a protocol to assess asbestos-related risk. Washington, DC: US Environmental Protection Agency, 2003.

Bianchi, C., T. Bianchi, and M. Tommasi. 2007. Long latency periods in asbestos-related mesothelioma of the pleura. European Journal of Oncology. 12(3):189-195.

Blake, T. V. Castranova, D. Schwegler-Berry, P. Baron, G.J. Deye, C. Li, and W. Jones. 1998. Effect of fiber length on glass fiber microfiber cytotoxicity. Journal of Toxicology and Environmental Health Part A 54:243-259.

Bocchetta, I. Di Resta, A. Powers, R. Fresco, A. Tosolini, J.R. Testa, H.I. Pass, P. Rizzo, and M. Carbone. 2000. Human mesothelial cells are unusually susceptible to simian virus 40-mediated transformation and asbestos cocarinogenicity. Proceedings of the National Academy of Sciences of the United States of America 97(18):10214-10219.

Bocchetta, M. S. Eliasz, M.A. De Marco, J. Rudzinski, L. Zhang, and M. Carbone. 2008. The SV40 large T-antigen-p53 complexes bind and activate the insulin-like growth factor-I promoter stimulating cell growth. Cancer Research 68(4):1022-1029.

Bonaldi, T., F. Talamo, P. Scaffidi, D. Ferrera, A. Porto, A. Bachi, A. Rubartelli, A. Agresti, and M.E. Bianchi. 2003. Monocytic cells hyperacetylate chromatin protein HMBG1 to redirect it towards secretion. The EMBO Journal 22(20):5551-5560.

Boffetta, P. 2006. Human cancer from environmental pollutants: The epidemiological evidence. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 608(2):157-162.

Broaddus, V.C., L. Yang, L.M. Scavo, J.D. Ernst, and A.M. Boylan. 1996. Asbestos induces apoptosis of human and rabbit pleural mesothelial cells via reactive oxygen species. Journal of Clinical Investigation 98:2050-2059.

Broaddus, V.C. and M-C. Jaurand. 2002. Asbestos Fibres and their Interaction with Mesothelial Cells *in vitro* and *in vivo*. In Robinson, B.W.S. and A.P. Chahinian, eds. *Mesothelioma*. Martin Dunitz Ltd, Florence, Kansas. 273-294 pp.

Carbone, M. H.I. Pass, P. Rizzo, M. Marinetti, M. Di Muzio, D.J. Mew, A.S. Levine, and A. Procopio. 1994. Simian virus40-like DNA sequences in human pleural mesothelioma. Oncogene 9(6):1781-1790.

Carbone, M., H.L. Bevan, R.F. Dodson, I. Pagano, P.T. Morris, U.A. Dogan, A.F. Gazdar, H.I. Pass, and H. Yang. 2012. Malignant mesothelioma: facts, myths and hypotheses. Journal of Cellular Physiology 227(1):44-58.

Carbone, M., R.A. Karzke, and J.R. Testa. 2002. The pathogenesis of mesothelioma. Seminars in Oncology. 29(1):2-17.

Carbone, M., S. Emri, A.U. Dogan, I. Steele, M. Tuncer, H.I. Pass, and Y.I. Baris. 2007. A mesothelioma epidemic in Cappadocia: scientific developments and unexpected social outcomes. Nature Reviews Cancer 7(2):147-154.

Churg, A. 1988. Chrysotile, tremolite, and malignant mesothelioma in man. Chest 93(3):621-628.

—. 1998. Neoplastic asbestos-induced disease. In Churg, A. and F.H.Y. Green, eds. *Pathology of Occupational Lung Disease*, 2nd edition. Williams and Wilkins, Baltimore, MD. 339-391 pp.

Cicala, C., F. Pompetti, and M. Carbone. 1993. SV40 induces mesothelioma in hamsters. The American Journal of Pathology 142(5):1524-1433.

Cullen, M.R. and R.S. Baloyi. 1991. Chrysotile asbestos and health in Zimbabwe, I: analysis of miners and millers compensated for asbestos-related diseases since independence (1980). American Journal of Industrial Medicine 19(2):161-169.

Cutrone, R., J. Lednicky, G. Dunn, P. Rizzo, M. Bocchetta, K. Chumakov, P. Minor, and M. Carbone. 2005. Some oral poliovirus vaccines were contaminated with infectious SV40 after 1961. Cancer Research 65(22):10273-10279.

Davis, J.M.G, J. Addison, R.E. Bolton, et al. 1986. The pathogenicity of long versus short fiber samples of amosite asbestos administered to rats by inhalation and intraperitoneal injection. British Journal of Experimental Pathology. 67(3):415-430.

Desai, R. and R.J. Richards. 1978. The adsorption of biological macromolecules by mineral dusts. Environmental Research 16(1-3):449-464.

Destro A, G.L. Ceresoli, M. Falleni, P.A. Zucali, E. Morenghi, P. Bianchi, C. Pellegrini, N. Cordani, V. Vaira, M. Allosio, A. Rizzi, S. Bosari, and M. Roncalli. 2006. EGFR overexpression in malignant pleural mesothelioma. An immunohistochemical and molecular study with clinico-pathological correlations. Lung Cancer 51(2):207-15.

Dogan, A.U. 2005. Malignant Mesothelioma and Erionite. In Pass, H.I., N.J. Vogelzang, and M. Carbone, eds. *Malignant Mesothelioma*. Springer Science+Business Media, Inc, New York, NY. 242-258 pp.

Dogan, M. and A.U. Dogan. 2005. Asbestos Mineralogy and Health Effects. In Pass, H.I., N.J. Vogelzang, and M. Carbone, eds. *Malignant Mesothelioma*. Springer Science+Business Media, Inc, New York, NY. 209-224 pp.

Donaldson, K., F. Murphy, A. Schinwald, R. Duffin, and C.A. Poland. 2011. Identifying the pulmonary hazard of high aspect ratio nanoparticles to enable their safety-by-design. Nanomedicine 6:143-156.

Donaldson, K., G.M. Brown, D. Brown, R.E. Bolton, and J.G. Davis. 1989. Inflammation generating potential of long and short fiber amosite asbestos samples. British Journal of Industrial Medicine 46:271-276.

EPA. 2012. Asbestos Laws and Regulations. United States Environmental Protection Agency. Available at http://www.epa.gov/asbestos/lawsregs.html. Accessed March 28, 2013.

Epidemiology of Mesothelioma. 2005. In Galateau-Salle, F., eds. *Pathology of Malignant Mesothelioma*. Springer-Verlag London Limited, China. 1-10 pp.

Fadeel, B., V. Kagan, H. Krug, A. Shvedeova, M. Svartengren, L. Tran, and L. Wiklund. 2007. There's plenty of room at the forum: potential risks and safety assessment of engineered nanomaterials. Nanotoxicology 1(2):73-84.

Fraire, A.E., S. Cooper, S.D. Greenberg, P. Buffler, and C. Langston. 1988. Mesothelioma of childhood. Cancer 62(4):838-847.

Fresco, R. 2005. Malignant Mesothelioma Electron Microscopy. In Pass, H.I., N.J. Vogelzang, and M. Carbone, eds. *Malignant Mesothelioma*. Springer Science+Business Media, Inc, New York, NY. 21-33 pp.

Gabrielson, E.W., J.F. Lechner, B.I. Gerwin, et al. 1991. Cultured human mesothelial cells are selectively sensitive to cell killing by asbestos and related fibres: a potential in vitro assay for carcinogenicity. In Brown, J.A.H.R.C. and N.F. Johnson, eds. *Mechanisms in Fibre Carcinogenesis*. Plenum Press, New York, NY. 505-511 pp.

Gan, L., E.F. Savransky, T.M. Fasy, and E.M. Johnson. 1993. Transfection of human mesothelial cells mediated by different asbestos fiber tyes. Environmental Research 62(1):28-42.

Gibas, Z., P.L. Frederick, K.H. Antman, S. Bernal, R. Stahel, and A.A. Sandberg. 1986. Chromosome changes in malignant mesothelioma. Cancer Genetics and Cytogenetics 20(3-4):191-201.

Goldberg, M. 2005. Preface. In Galateau-Salle, F., eds. *Pathology of Malignant Mesothelioma*. Springer-Verlag London Limited, China. v-vi pp.

Goldberg, M., E. Imbernon, P. Rolland, A.G.S. ilg, A. de Quillacq, C. Frenay, S Chamming's, P. Arveux, C. Boutin, J.C. Pairon, P. Astoul, F. Galateau-Salle., and P. Brochard. 2007. The French National Mesothelioma Surveillance Program. Journal of Occupational Medicine 63(6):390-395.

Goodman, J.E, M.A. Nascarella, and P.A. Valberg. 2009. Ionizing radiation: a risk factor for mesothelioma. Cancer Causes Control 20(8):1237-1254.

Hansen, K. and B. Mossman. 1987. Generation of superoxide (O_2^-) from alveolar macrophages exposed to asbestiform and non fibrous particles. Cancer Research 47:1681-1686.

Haque, A.K., D.M Vrazel, K.D. Burau, S.P. Cooper, and T. Downs. 1996. Is there transplacental transfer of asbestos? A study of 40 stillborn infants. Pediatric Pathology and Laboratory Medicine 16(6):877-92.

Harris, L.V. and I.A. Kahwa. 2003. Asbestos: old foe in 21st century developing countries. Science of the Total Environment 307(1-3):1-9.

Harris, R.L., Jr. and V. Timbrell. 1977. The influence of fiber shape in lung deposition: mathematical estimates, pp. 75-89. In Walter, W.H., ed. *Inhaled Particles*, Vol. IV, Part 1. Pergamon Press, Oxford.

Heintz, N.H., Y.M. Janssen-Heininger, and B.T. Mossman. 2010. Asbestos, lung cancers, and mesotheliomas: from molecular approaches to targeting tumor survival pathways. American Journal of Respiratory Cell and Molecular Biology 42:133-139.

Hesterberg, T.W., G. Chase, C. Axten, W.C. Miller, R.P. Musselman, O. Kamstrup, J. Hadley, C. Morscheidt, D.M. Bernstein, and P. Thevenaz. 1998. Biopersistence of synthetic vitreous fibers and amosite asbestos in the rat lung following inhalation. Toxicology and Applied Pharmacology 151(2):262-275.

Hillerdal, G. 1983. Malignant mesothelioma 1982: review of 4710 published cases. British Journal of Diseases of the Chest 77:321-343.

—. 1999. Mesothelioma: cases associated with non-occupational and low dose exposures. Occupational and Environmental Medicine 55:1968-1972.

Hodgson, J.T. and A. Darnton. 2000. The quantitative risks of mesothelioma and lung cancer in relation to asbestos exposure. The Annals of Occupational Hygiene 44(8):565-601.

Hughes, J.M. and H. Weill. 1986. Asbestos Exposure-Quantitative Assessment of Risk. American Review of Respiratory Disease. 133(1):5-13

Husain, A.N., T.V. Colby, N.G. Ordonez, T. Krausz, A. Borczuk, Cagle, L.R. Chirieac, A. Churg, F. Galateau-Salle, A.R. Gibbs, A.M. Gown, S.P. Hammar, L.A. Litzky, V.L Roggli, W.D. Travis, and M.R. Wick. 2009. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. Archives of Pathology and Laboratory Medicine 133(8):1317-1331.

Ilgren, E.B., F.D. Pooley, J.C. Larragoitia, M. Talamantes, G.L. Navarrete, E. Krauss, and A.F. Brena. 2008. First confirmed erionite related mesothelioma in North America. Indoor and Built Environment 0(0):1-2.

Ismail-khan, R., L.A. Robinson, C.C. Williams Jr., C.R. Garrett, G. Bepler, and G.R. Simon. 2006. Malignant pleural mesothelioma: a comprehensive review. Cancer Control 13(4):255-263.

Jasani, B., A. Cristaudo, S.A. Emri, A.F. Gazdar, A. Gibbs, B. Krynska, C. Miller, L. Mutti, C. Radu, M. Tognon, and A. Procopio. 2001. Association of SV40 with human tumours. Seminars in Cancer Biology 11(1):49-61.

Jaurand, M.-C., H. Kaplan, J. Thiollet, M.-C. Phinchon, J.-F. Benaudin and j. Bignon. 1979. Phagocytosis of chrysotile fibres by pleural mesothelial cells in culture. American Journal of Pathology 94(3):529-538.

Jaurand, M.-C., P. Baillif, J.-H. Thomassin, L. Magne, and J.-C. Touray. 1983. X-ray photoelectron spectroscopy and chemical study of the adsorption of biological molecules on chrysotile asbestos surface. Journal of Colloid and Interface Science 95(1):1-9.

Kagan, V.E., H. Bayir, and A.A. Shvedova. 2005. Nanomedicine and nanotoxicology: two sides of the same coin. Nanomedicine 1(4):313-316.

Kinnula, V.L. 1999. Oxidant and antioxidant mechanisms of lung disease caused by asbestos fibres. European Respiratory Journal 14(3):706-716.

Kliment, C.R., K. Clemens, and T.D. Oury. 2009. North American erionite-associated mesothelioma with pleural plaques and pulmonary fibrosis: a case report. International Journal of Clinical and Experimental Pathology 2(4):407-410.

Kordossis, T., O. Kosmospoulou, J. Zagoreos, T. Dossios, I. Deladetsima, N. Tsavaris, N. Sipsas, J. Stratigos, and K. Papavassiliou. 1994. Malignant mesothelioma in an HIV-positive patient. AIDS 8(3):394-395.

Kroczynska, B., R. Cutrone, M. Bocchetta, H. Yang, A.G. Elmishad, P. Vacek, M. Ramos-Nino, B.T. Mossman, H.I. Pass, and M. Carbone. 2006. Crocidolite asbestos and SV40 are cocarcinogens in human mesothelial cells and in causing mesothelioma in hamsters. Proceedings of the National Academy of Sciences of the United States of America 103(38):14128-14133.

Lanphear, B.P. and C.R. Buncher. 1992. Latent period for malignant mesothelioma of occupational origin. Journal of Occupational Medicine 34(7):718-721.

Liu, J.Y., D.M. Brass, G.W. Hoyle, and A.R. Brody. 1998. TNF-alpha receptor knockout mice are protected from the fibroproliferative effects of inhaled asbestos fibers. American Journal of Pathology 153(6):1839-1847.

Macmillian Cancer Support. 2010. What is Mesothelioma? Macmillian Cancer Support. Available at http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Mesothelioma/Aboutmesothelioma/Whatismesothelioma.aspx. Accessed April 27, 2013.

McDonald, J.C., F.D.K. Liddell, A. Dufresne, and A.D. McDonald. 1993. The 1891-1920 birth cohort of Quebec chrysotile miners and millers: mortality 1976-88. British Journal of Industrial Medicine 50:1073-1081.

McDonald, J.C., F.D.K. Liddell, G.W. Gibbs, G.E. Eyssen, and A.D. McDonald. 1980. Dust exposure and mortality in chrysotile mining, 1910-1975. British Journal of Industrial Medicine 37:11-24.

McDonald, J.C. and A. McDonald. 2005. Mesothelioma and Asbestos Exposure. In Pass, H.I., N.J. Vogelzang, and M. Carbone, eds. *Malignant Mesothelioma*. Springer Science+Business Media, Inc, New York, NY. 267-292 pp.

McDonald, J.C. and A.D McDonald. 1997. Chrysotile, tremolite and carcinogenicity. British Occupational Hygiene Society 41(6):699-705.

Molecular Biology. 2005. In Galateau-Salle, F., eds. *Pathology of Malignant Mesothelioma*. Springer-Verlag London Limited, China. 1-10 pp.

Monchaux, G., J.P. Morlier, M. Morin, J. Charmeaud, J. Lafuma, and R. Masse. 1994. Carcinogenic and Cocarcinogenic Effects of Radon and Radon Daughters in Rats. Environmental Health Perspectives 102(1):64-73.

Mossman, B.T., D.W. Kamp, and S.A. Weitzman. 1996. Mechanisms of carcinogenesis and clinical features of asbestos-associated cancers. Cancer Investigation 14(5):466-480.

Nakamura, E, A. Makishima, K. Hagino, and K. Okabe. 2009. Accumulation of radium in ferruginous protein bodies formed in lung tissue: association of resulting radiation hotspots with malignant mesothelioma and other malignancies. Proceedings of the Japan Academy Series B-Physical and Biological Sciences 85(7):229-239.

Neugut, A.I., H. Ahsan, and K.H. Antman. 1997. Incidence of malignant pleural mesothelioma following exposure after thoracic radiotherapy. Cancer 80:948-50.

Olofsson, K. and J. Mark. 1989. Specificity of asbestos-induced chromosomal aberrations in short-term cultured human mesothelial cells. Cancer Genetics and Cytogenetics 41(1):33-39.

Occupational Safety and Health Administration. 1992. Occupational Exposure to Asbestos, Tremolite, Anthophyllite, and Actinolite. United States Department of Labor. Available at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=PREAMBLES&p_id=787. Accessed April 28, 2013.

Pacurari, M. X. Yin, J. Zhao, M. Ding, S.S. Leonard, D. Schwegler-Berry, B.S. Ducatman, D. Sbarra, M.D. Hoover, V. Castranova, and V. Vallyathan. 2008. Raw single-wall carbon nanotubes induced oxidative stress and activate MAPKs, AP-1, NF-Kb, and aKT in normal and malignant human mesothelial cells. Environmental Health Perspectives 116(9):1211-1217.

Palomaki, J., E. Valimaki, J. Sund, M. Vippola, P.A. Clausen, K.A. Jensen, K. Savolainen, S. Matikainen, and H. Alenius. 2011. Long, Needle-like Carbon Nanotubes and Asbestos Activate the NLRP3 Inflammasome through a Similar Mechanism. ACS Nano 5(9):6861-6870.

Poland, C.A., R. Duffin, I. Kinloch, A. Maynard, W.A.H. Wallace, A. Seaton, V. Stone, S. Brown, W. MacNee, and K. Donaldson. 2008. Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nature Nanotechnology 3(7):423-428.

Popescu, N.C., A.P. Chahinian, and J.A. DiPaolo. 1988. Nonrandom chromosome alterations in human malignant mesothelioma. Cancer Research 48(1)-142-147.

Ramos-Nino, M.E., M. Martinelli, L. Scapoli, and B.T. Mossman. 2005. Asbestos-Induced Mesothelioma. In Pass, H.I., N.J. Vogelzang, and M. Carbone, eds. *Malignant Mesothelioma*. Springer Science+Business Media, Inc, New York, NY. 21-33 pp.

Report of the expert panel on health effects of asbestos and synthetic vitreous fibers: the influence of fiber length. Washington, DC: Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services, 2003.

Roggli, V.L., T.D. Oury, and E.J. Moffatt. 1997. Malignant mesothelioma in women. Anatomic Pathology 2:147-163.

Roushdy-Hammady, I., I Siegel, S. Emri, J.R. Testa, and M. Carbone. 2001. Genetic-susceptibility factor and malignant mesothelioma in the Cappadocian region of Turkey. The Lancet 357(9254): 444-445.

Ryman-Rasmussen, J.P., M.F. Cesta, A.R. Brody, J.K. Shipley-Philips, J.I. Everitt, E.W. Tewksbury, O.R. Moss, B.A. Wong, D.E. Dodd, M.E. Andersen and J.C. Bonner. 2009. Inhaled Carbon Nanotubes Reach the Subpleural Tissue in Mice. Nature Nanotechnology 4(11): 747-751.

Saffinotti, U. 2005. Mesothelioma Carcinogenesis: In Vivo Models. In Pass, H.I., N.J. Vogelzang, and M. Carbone, eds. *Malignant Mesothelioma*. Springer Science+Business Media, Inc, New York, NY. 60-86 pp.

Sartore-Bianchi, A. F. Gasparri, A. Galvani, L. Nici, J.W. Darnowski, D. Barbone, D.A. Fennell, G. Gaudino, C. Porta, and L. Mutti. 2007. Bortezomib inhibits nuclear-kappaB dependent survival and has potent *in vivo* activity in mesothelioma. Clinical Cancer Research 13:5942-5951.

Shukla, A. J.M. Miller, C. Cason, M. Sayan, MB. MacPherson, S.L. Beuschel, J. Hillegass, P.M. Vacek, H.I. Pass, and B.T. Mossman. 2013. Extracellular signal regulated kinase 5: a potential therapeutic target for malignant mesotheliomas. Clinical Cancer Research, In press.

Shukla, A. T.F. Barrett, K.I. Nakayama, K. Nakayama, B.T. Mossman, and K.M. Lounsbury. 2006. Transcriptional up-regulation of MMP12 and MMP13 by asbestos occurs via a PKCdelta-dependent pathway in murine lung. FASEB Journal 20:997-999.

Shvedova, A.A., E.R. Kisin, D. Porter, P. Schulte, V.E. Kagan, B. Fadeel, and V. Castranova. 2009. Mechanisms of pulmonary toxicity and medical applications of carbon nanotubes: Two faces of Janus? Pharmacology and Therapeutics 121:192-204.

Skinner, H.C.W., M. Ross, and C. Frondel. 1988. Asbestos and Other Fibrous Materials. Oxford University Press, New York, NY. 204 pp.

Spirtas, R, E.R. Heineman, L. Bernstein, G.W. Beebe, R.J. Keehn, A. Stark, B.L. Harlow, and J. Benichou. 1994. Malignant mesothelioma: attributable risk of asbestos exposure. Occupational and Environmental Medicine 51(12):804-811.

Sprynskyy, M., J. Niedojadło, and B. Buszewski. 2011. Structural features of natural and acids modified chrysotile nanotubes. Journal of Physics and Chemistry of Solids 72:1015-1026.

Stanton, M.F., M. Layard, A. Tegeris, et al. 1981. Relation of particle dimension to carcinogenicity in amphibole asbestos and other fibrous minerals. Journal of the National Cancer Institue 67:965-975.

Stayner, L.T., D.A. Dankovic, and R.A. Lemen. 1996. Occupational Exposure to Chrysotile Asbestos and Cancer Risk: A Review of the Amphibole Hypothesis. American Journal of Public Health. 86(2):179-186.

Stewart, H.L., C.J. Buchner, and E.H. Coleman. 1931. Asbestosis: report of two cases. Archives of Pathology. 12(6):909-916.

Strohmeier, B.R., J.C. Huntington, K.L. Bunker, M.S. Sanchez, K. Allison, and R.J. Lee. 2010. What is asbestos and why is it important? Challenges of defining and characterizing asbestos. International Geology Review 52(7-8):801-872.

Takagi, A., A. Hirose, T. Nishimura, N. Fukumori, A. Ogata, N. Ohashi, S. Kitajima, and J. Kanno. 2009. Induction of mesothelioma in p53+/- mouse by intraperitoneal application of multi-wall carbon nanotube. Journal of Toxicological Sciences 33(1):105-116.

UofMHealth.org. 2013. Ovarian Germ Cell Tumors Treatment (PDQ®): Treatment – Patient Information [NCI]. University of Michigan Health System. Available at http://www.uofmhealth.org/health-library/ncicdr0000062967#ncicdr0000062967-general-information-about-ovarian-germ-cell-tumors. Accessed April 27, 2013.

US Code of Federal Regulations. 2003. Protection of the Environment, Toxic Substances Control Act, Asbestos. 40 CFR 763.

Wagner, J.C.. 1997. Asbestos-Related Cancer and the Amphibole Hypothesis. American Journal of Public Health 87(4):687-688.

Wagner, J.C., C.A. Sleggs, and P. Marchand. 1960a. Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. British Journal of Industrial Medicine 17(4):260-271.

—. 1960b. The role of environmental carcinogens, viruses, and genetic predisposition in the pathogenesis of mesothelioma. Cancer Biology and Therapy 1(4):350-355.

Wagner, J.C., J.W. Skidmore, R.J. Hill, and D.M. Griffiths. 1985. Erionite exposure and mesotheliomas in rats. British Journal of Cancer 51(5):727-730.

Woodworth, C.D., B.T. Mossman, and J.E. Craighead. 1983. Induction of squamous metaplasia in organ cultures of hamster trachea by naturally occurring and synthetic fibers. Cancer Research 43:4906-4912.

Yang, H., Z. Rivera, S. Jube, M. Nase, P. Bertino, C. Goparaju, G. Franzoso, M.T. Lotze, T. Krausz, H.I. Pass, M.E. Bianchi, and M. Carbone. 2010. Programmed necrosis induced

by asbestos in human mesothelial cells causes high-mobility group box 1 protein release and resultant inflammation. Proc Natl Acad Sci USA 107(28):12611-12616.

Zanella, C.L., C.R. Timblin, A. Cummins, M. Jung, J. Goldberg, R. Raabe, T.R. Tritton, and B.T. Mossman. 1996. Asbestos-induced phosphorylation of epidermal growth factor receptor is linked to c-fos and apoptosis. American Journal of Physiology 277:L684-L693.

Zanella, C.L., J. Posada, T.R. Tritton, and B.T. Mossman. 1996. Asbestos causes stimulation of the extracellular signal-regulated kinase 1 mitogen-activated protein kinase cascade after phosphorylation of the epidermal growth factor receptor. Cancer Research 56:5334-5338.

Ziegler, A. C.A. Seemayer, M. Hinterberger, P. Vogt, C. Bigosch, O. Gautschi, L. Tornillo, D.C. Betticher, H. Moch, and R.A. Stahel. 2007. Low prevalence of SV40 in Swiss mesothelioma patients after elimination of false-positive PCR results. Lung Cancer 57(3):282-291.