NONPULMONARY OUTCOMES OF ASBESTOS EXPOSURE

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The adverse pulmonary effects of asbestos are well accepted in scientific circles. However, the extrapulmonary consequences of asbestos exposure are not as clearly defined. In this review the potential for asbestos to produce diseases of the peritoneum, immune, gastrointestinal (GIT), and reproductive systems are explored as evidenced in published, peer-reviewed literature. Several hundred epidemiological, in vivo, and in vitro publications analyzing the extrapulmonary effects of asbestos were used as sources to arrive at the conclusions and to establish areas needing further study. In order to be considered, each study had to monitor extrapulmonary outcomes following exposure to asbestos. The literature supports a strong association between asbestos exposure and peritoneal neoplasms. Correlations between asbestos exposure and immune-related disease are less conclusive; nevertheless, it was concluded from the combined autoimmune studies that there is a possibility for a higher-than-expected risk of systemic autoimmune disease among asbestos-exposed populations. In general, the GIT effects of asbestos exposure appear to be minimal, with the most likely outcome being development of stomach cancer. However, IARC recently concluded the evidence to support asbestos-induced stomach cancer to be “limited.” The strongest evidence for reproductive disease due to asbestos is in regard to ovarian cancer. Unfortunately, effects on fertility and the developing fetus are under-studied. The possibility of other asbestos-induced health effects does exist. These include brain-related tumors, blood disorders due to the mutagenic and hemolytic properties of asbestos, and peritoneal fibrosis. It is clear from the literature that the adverse properties of asbestos are not confined to the pulmonary system.

For this review, several hundred epidemiological, in vivo, and in vitro publications analyzing the extrapulmonary effects of asbestos were used as sources to (1) arrive at the conclusions and (2) establish areas needing further study. In order to be considered, each study had to monitor extrapulmonary outcomes following exposure to asbestos. Papers were identified using keyword searches focusing on the term “asbestos” and its subtypes. Therefore, differences in author interpretations of what qualifies as asbestos may exist. Only primary epidemiological studies were used to reach the conclusions; however, reports analyzing multiple cohort studies are discussed when appropriate. For animal studies, inhalation experiments were only included if nonpulmonary outcomes are reported. Similarly, only in vitro studies utilizing cells that were not isolated from the pulmonary system are included. When possible, the type of asbestos exposure is incorporated into the discussion in order to establish differences in the extrapulmonary effects of chrysotile versus the amphiboles.

Route of exposure is also an important consideration in evaluating the extrapulmonary effects of asbestos. Although traditionally considered to be an inhaled toxicant, asbestos...
exposure might also occur through ingestion of contaminated food and water. Other potential routes of exposure include transplacental transfer and introduction to the reproductive system during coitus. When feasible, differences in route of exposure and resulting outcomes are discussed.

In compiling the literature referenced in this article, it was necessary to depend on the authors’ interpretations and conclusions from the data. Therefore, a significant limitation of this review is our reliance on the reported outcomes from each study. However, each paper was published as part of a peer-review process and when the papers are as a whole they should represent the best evidence available. In addition, there is a paucity of data examining some of the extrapulmonary effects. For example, although transplacental transfer of asbestos appears to occur, there are an appreciably limited number of publications addressing the issue. As a consequence, the scarcity in the number of studies is also a limitation of this report. In addition, there are broad discrepancies in the conclusions drawn from the various studies. These differences are discussed when needed. Finally, the vast majority of these studies focus on the effects of chrysotile and/or crocidolite exposure. However, there are reports of other amphiboles being associated with development of various cancer types. The limited number of these studies makes it difficult to draw conclusions; however, their potential to cause disease may be significant.

**PERITONEAL EFFECTS OF ASBESTOS**

Mesothelioma, which most commonly occurs in the pleural space of the lung followed by the peritoneum, is primarily linked to asbestos exposure (Boffetta, 2007). Peritoneal mesothelioma (PM) is the most common neoplasm of the peritoneum (Mack, 1995) and along with pleural mesothelioma was recently attributed to an expected survival time of 7.6 and 13.5 mo for males and females following diagnosis, respectively. With mesothelioma described as an “aggressive neoplasm that rapidly spreads within the confines of the abdominal cavity to involve most accessible peritoneal and omental surfaces,” treatment regimes are largely unsuccessful (Hesdorffer et al., 2008). Consequently, prevention remains the best option for managing PM. Therefore, an understanding of the temporal and dose-response aspects associated with the development of the disease remains a critical task of the scientific community.

**Epidemiological Evidence**

It is widely accepted that asbestos exposure results in an increased risk for peritoneal cancers in general and mesothelioma, specifically (Armstrong et al., 1984; Boffetta, 2007; Welch et al., 2005; McDonald et al., 2006; Sluis-Cremer et al., 1992; Browne and Smither, 1983; Selikoff et al., 1984; Ribak et al., 1988). There are a number of asbestos-exposed cohorts with a documented link to cancer, including PM. For example, studies on an Australian cohort of crocidolite-exposed workers from the Wittenoom factory reported increased rates of peritoneal cancer (Berry et al., 2004; de Klerk et al., 1989; Reid et al., 2005; Musk et al., 1989), which remain consistent in Italian workers who later resettled in Italy (Merler et al., 2000). In addition, Canadian factory workers exposed primarily to chrysotile, with minor exposures to crocidolite, demonstrated an increased incidence of PM (McDonald, 1980). However, in the Canadian study, the risk was found to be less severe in workers only exposed to chrysotile as compared to a mixed exposure. Furthermore, a later study by McDonald et al. (1997), found no cases of peritoneal mesothelioma in a large cohort of Canadian workers exposed primarily to chrysotile. Consequently, evidence suggests that crocidolite is a more potent inducer of PM than chrysotile alone. In addition to chrysotile and crocidolite, amosite has been associated with a significant number of PM cases in a cohort of exposed workers (Ribak et al., 1989).

It is becoming increasingly apparent that the type of asbestos exposure has some influence on the location and possibly severity
of any developing neoplasm. While chrysotile fibers were detected in peritoneal mesotheliomas from North American insulation workers (Kohyama & Suzuki, 1991), in a study of Norwegian asbestos-cement workers primarily exposed to chrysotile, no peritoneal mesotheliomas were reported (Ulvestad et al., 2002). In addition, further analysis of Australian mesothelioma cases reported that higher lung fiber burdens (as measured by light microscopy (LM) and analytic transmission electron microscopy (TEM) with energy-dispersive x-ray analysis (EDXA) are associated with a greater risk for peritoneal tumors for all fiber types except chrysotile (Leigh et al., 1991). Therefore, it is highly likely that crocidolite (and possibly other amphibole) exposure poses the greatest threat for development of peritoneal tumors, including mesothelioma. In addition, fiber size appears to be an important factor in the carcinogenicity of asbestos. In a study using high-resolution analytical electron microscopy to determine the dimensions of asbestos fibers in 168 cases of mesothelioma, the majority of the fibers were shorter than 5 μm in length (Suzuki & Yuen, 2002).

Type and Route of Exposure

The type of asbestos exposure (i.e., chrysotile versus crocidolite and other amphiboles) appears to play an important role in the development of peritoneal neoplasms. While there is some evidence linking chrysotile asbestos with peritoneal tumors, it is evident from the literature that occupational exposure to crocidolite asbestos with peritoneal tumors, it is evident from the literature that occupational exposure to crocidolite asbestos with peritoneal tumors, it is evident from the literature that occupational exposure to crocidolite asbestos with peritoneal tumors, it is evident from the literature that occupational exposure to crocidolite asbestos with peritoneal tumors, it is evident from the literature that occupational exposure to crocidolite asbestos with peritoneal tumors, it is evident from the literature that occupational exposure to crocidolite asbestos with peritoneal tumors, it is evident from the literature that occupational exposure to crocidolite asbestos with peritoneal tumors, it is evident from the literature that occupational exposure to crocidolite asbestos with peritoneal tumors, it is evident from the literature that 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The precise pathway resulting in peritoneal exposure to asbestos is not clear, as there is no known mechanism for direct contact. However, based on studies suggesting systemic distribution of asbestos following inhalation and ingestion, it is likely that direct contact does occur. Furthermore, it is possible that activation of signaling cascades initiated in the lung affect disease in the peritoneum. Specifically, transforming growth factor-beta (TGF-β) was implicated in asbestos-induced disease. A recent examination of an asbestos cohort revealed that serum levels of TGF-β were found to correlate well with peritoneal disease severity, increasing approximately 2.4-fold from ILO radiographic category 0 to category 3 (Li et al., 2009).

Animal Studies

Rodents have commonly provided a reliable model for studying the peritoneal effects of asbestos. Reports describing development of peritoneal tumors in mice (Suzuki & Kohyama, 1984; Branchaud et al., 1989) and rats (Adachi et al., 2001; Davis and Jones, 1988; Unfried et al., 1997; Craighead et al., 1987; Cullen et al., 2002; Minardi & Maltoni, 1988) are relatively abundant. In addition, attempts at elucidating mechanisms have uncovered clues as to the development of asbestos-induced peritoneal tumors. In general, administration of crocidolite (ip) appears to result in fiber aggregates in peritoneal macrophages, exudate cells and fibrous tissue—eventually developing into granulomas (Koerten et al., 1990). In mice, crocidolite fibers recovered via bleach digestion and analyzed by stereomicroscopy, scanning electron microscopy, and/or autoradiography (Moalli et al., 1987; Macdonald & Kane, 1997) from the peritoneal lining do not decline in number as much as 6 mo following ip administration. The biopersistent properties of crocidolite resulted in chronic inflammation and mesothelial cell proliferation. In addition, crocidolite administered to rats ip resulted in decreased adhesion of peritoneal mesothelial
cells (Lee et al., 1993). In these rats, the normal microvillous surface of the mesothelium was replaced with proliferating mesothelial cells within 7 d of exposure.

In mice, crocidolite ip given in doses ranging from $10^4$ to $10^8$ fibers resulted in a dose-dependent recruitment of inflammatory cells to the peritoneal cavity (Cullen et al., 2000). These stimulated macrophages show increased concentrations of iron (Fe) in both the lysosome and cytoplasm, suggesting an increase in oxidative potential (Koerten et al., 1986) (for additional information see Aust et al., this issue). Further, 100% of rats given a single ip injection of de-ironized crocidolite plus Fe supplements developed peritoneal mesotheliomas, whereas only 40% and 50% developed mesotheliomas when given de-ironized crocidolite or unmodified crocidolite alone, respectively (Adachi et al., 1994). It is evident, therefore, that Fe plays a role in crocidolite’s carcinogenic potential, likely due to an increase in oxidative stress. In fact, the mutagenic potential of asbestos is thought to at least be partially due to oxygen radicals, as its mutagenicity is reduced by antioxidants in human whole blood lymphocytes (Korkina et al., 1992) (for additional information see Hei et al., this issue). Moreover, growth of chrysotile-induced lung carcinomas transplanted into the peritoneal cavity of mice is inhibited by treatment with trans-retinoic acid by 58–64% (Hubert et al., 1983).

It is likely that the carcinogenic effects of asbestos are linked to mutations in certain genes in addition to chromosomal aberrations (CA). For example, ip administration of chrysotile in mice results in an increase in the level of damaged chromosomes in peritoneal cells (Durnev et al., 1993). Moreover, chrysotile induced CA in human lymphocytes, whole blood cultures, peritoneal fluid, and bone-marrow cells in mice (Durnev et al., 1993). In addition, heterozygous transgenic Nf2$^{−/−}$ mice showed accelerated development of peritoneal mesotheliomas following crocidolite exposure (Kane, 2006; Fleury-Feith et al., 2003). Tumors from these mice also demonstrated frequent homozygous deletions of the Cdkn2a/Arf locus and adjacent Cdkn2b tumor suppressor gene (Altomare et al., 2005) (for additional information see Testa et al., this issue). Finally, TP53$^{−/−}$ mice given a weekly ip injection of UICC crocidolite showed an increased incidence and decreased latency of peritoneal mesothelioma development (Vaslet et al., 2002).

### In Vitro Studies

A significant body of literature has accumulated using peritoneal macrophages and other cell lines to study the mechanisms of asbestos-induced disease. It is known that applying crocidolite or chrysotile to lavaged peritoneal macrophages results in protrusion of fibers from membrane-bound vacuoles, as well as free in the cytoplasm and penetrating the nucleus, as seen by both scanning electron microscopy (SEM) and TEM (Johnson and Davies, 1981). The role of Fe in asbestos toxicity has also been studied in vitro. The ability of mouse peritoneal macrophages to take up UICC crocidolite is dependent on fiber size and availability of Fe as measured by either LM or TEM (Koerten et al., 1990). Specifically, small fibers were internalized and long fibers were left to form asbestos bodies in an Fe-dependent manner. Furthermore, crocidolite-stimulated nitric oxide synthase (NOS) activity and expression in murine glial cells was inhibited by Fe supplementation and enhanced by Fe chelation (Aldieri et al., 2001). Due to the ability of Fe to generate free radicals, in vitro tests were conducted to determine whether oxidative stress played a role in the toxicity of asbestos. Indeed, when mouse peritoneal macrophages were incubated with crocidolite, reactive oxygen metabolites were released (Goodglick & Kane, 1986). The free-radical-generating ability of chrysotile may be prevented in the presence of antioxidants. Specifically, in rat peritoneal macrophages, a decrease in phagocytosis, cell injury, and lactate dehydrogenase (LDH) activity release was observed when cells were exposed to flavonoids along with chrysotile (Kostyuk & Potapovich, 1998). The flavonoids quercetin, dihydroquercetin, and...
rutin were effective in the same order as their superoxide scavenging potential. In addition, metal-complexed flavonoids with improved radical scavenging ability are more potent in their protective effects against natural chrysotile (Tuva, Russia) toxicity (Kostyuk et al., 2001). Similarly, green tea extracts protected peritoneal macrophages and red blood cells from chrysotile toxicity (Kostyuk et al., 2000).

Modulation of the immune functions following asbestos exposure has also been examined using cultured peritoneal macrophages. Addition of chrysotile to these cells stimulated the release of lymphocyte-activating factors (Godelaine & Beaufay, 1989) as well as plasminogen activator, which was prevented by the addition of low concentrations of anti-inflammatory steroids (Hamilton, 1983).

**Summary**

The association between asbestos exposure and peritoneal neoplasms, specifically mesothelioma, has been well established (see Table 1). It is becoming increasingly apparent that crocidolite poses a greater risk for development of disease than chrysotile, and this risk is proportional to amount and duration of exposure. However, this issue remains unresolved due to the extremely toxic properties of chrysotile in vitro.

In summary the following were concluded:

- Occupational exposure to crocidolite and other amphiboles poses the greatest risk for development of peritoneal tumors as compared to chrysotile.
- Risk increases in a dose-dependent manner.
- Studies suggest that changes in iron overload resulting in increased oxidative stress is an important mechanism attributable to the development of asbestos-induced peritoneal cancer.
- Fiber size may affect in vitro effects due to differences in internalization, but more data is needed.

The following are areas that need further study:

- The role of an antioxidant-poor diet in the development of asbestos-induced peritoneal tumors.
- Genetic factors that may be important in development of disease.
- Impact of mineral composition of fibers.
- Translocation of asbestos fibers to the peritoneum and/or other possible signaling mechanisms involved in disease development.

### TABLE 1. Publications on Asbestos-Induced Peritoneal Disease

| Endpoint                  | Fiber type   | Human (Occupational) | Human (water/ingested) | Animal (inhalation) | Animal (ip) |
|---------------------------|--------------|----------------------|------------------------|---------------------|-------------|
| Peritoneal mesothelioma   | Chrysotile or mixed | 2(−)                 |                        | 4(+)               |             |
|                           | Crocidolite  | 9(+)                 |                        | 4(+)               |             |
|                           | Unknown      | 2(+)                 |                        | 1(−)               |             |
|                           | Amosite      |                      |                        |                    | 1(+)        |
| Peritoneal cancer (general) | Chrysotile  | 1(+)                 | 1(+)                   | 1(−)               |             |
|                           | Crocidolite  |                      |                        |                    | 1(+)        |
| Peritoneal fibrosis       | Chrysotile   | 1(+)                 |                        |                    |             |

Note. The number indicates how many articles were found with a positive (+) or negative (−) association between asbestos and disease. "Unknown" exposures indicate the data came from occupational exposure matrices, including textiles, insulation, or cement workers. Sources: aUlvestad, 2002; Albin, 1990. bAdachi, 2001; Davis, 1988; Minardi, 1988; Suzuki, 1984. cArmstrong, 1984; de Klerk, 1989b; Reid, 2005; Browne, 1983; McDonald, 2006; Musk, 1989; Sluis-Cremer, 1992; McDonald, 1997; Merler, 2000. dMinardi, 1988; Adachi, 1994; Branchaud, 1989; Cullen, 2002. eRibak, 1988; Selikoff, 1984. fLumley, 1976. gSuzuki, 1984. hPira, 2009. iKanarek, 1980. jBoorman, 1984. kKoerten, 1990b. lBateman, 1982. mWirth, 1975.
AUTOIMMUNE EFFECTS OF ASBESTOS

Although it has become fairly well accepted that specific systemic autoimmune diseases (SAID) such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and rheumatoid arthritis (RA) are associated with silica exposure, asbestos exposure has not yet been strongly linked with any particular autoimmune or connective tissue disorder. There are several possibilities for this knowledge gap, including a lack of statistical power due to relatively small or diffuse exposure cohorts, exposure assessment problems, the latency of the clinical disease, and mild clinical or subclinical entities that remain undetected or masked by other pathologies. It is also possible that asbestos exposure poses a very low risk of autoimmune pathology despite the presence of the characteristic autoantibodies. Nevertheless, the data are convincing in that there are immune abnormalities and humoral indices consistent with autoimmune mechanisms, including a variety of autoantibodies such as antinuclear antibodies (ANA), rheumatoid factor (RF), and a general increase in serum immunoglobulin (Ig) of the IgG and IgA classes.

Epidemiological Evidence

Asbestos exposure and autoantibodies
There are fewer than 100 epidemiological studies that have explored an association between asbestos exposure and SAID (see Table 2). However, studies of the humoral responses following asbestos exposure appear in the literature beginning around 1965 when the presence of RF and ANA was reported in asbestos workers (Pernis et al., 1965). Several subsequent studies also found increased frequency of positive RF tests in asbestos workers compared to controls (Turner-Warwick & Parkes, 1970; Stansfield & Edge, 1974; Lange

| Endpoint | Primary exposure (if known) | Type of exposure | Human studies | Animal studies | Case study |
|----------|-----------------------------|-----------------|--------------|---------------|-----------|
| Rheumatoid arthritis | Unknown | Occupational (e.g., cement worker) | 1(+)^a, 1(−)^b | 1(+)^c |
| SLE or lupus-like | Amphibole (Libby) | Occup/environ | 1(+)^d |
| Scleroderma | Tremolite | Pulmonary instillation | 1(+)^d, 1(−)^b |
| Scleroderma | Amphibole | Occupational | 1(+)^d, 1(−)^b |
| Autoimmune vasculitis | Chrysotile, amphibole | Occupational | 1(+)^d |
| Interstitial pneumonia | Chrysotile | Occupational | 1(−)^b, 1(−)^b |
| Autoantibodies ANA | chrysotile | Occupational, intrathracheal | 1(−)^d |
| Autoantibodies ANA | Tremolite | Occupational, intrathracheal | 1(−)^d, 1(−)^b |
| Autoantibodies ANA | Various | Occupational | 1(−)^d |
| Autoantibodies IgM Rh factor | chrysotile | Occupational | 1(−)^d |
| Autoantibodies IgM Rh factor | Amphibole | Occupational | 1(−)^d |
| Rheumatoid, nonspecific | Mixed (chrysotile and amphiboles) | Occupational | 1(−)^d, 1(−)^b |

Note. The number indicates how many articles were found with a positive (+) or negative (−) association between asbestos and disease. ^aOlsson, 2004. ^bGold, 2007. ^cGreaves, 1979. ^dNoonan, 2006. ^ePfau, 2008. ^fGold, 2007; Noonan, 2006. ^gRihova, 2005; Inoue, 2004. ^hStratta, 2001. ^iRihova, 2005. ^jInoue, 2004. ^kTurner-Warwick, 1970. ^lZerva, 1989. ^mPfau, 2005; Nigam, 1993; Tamura, 1993; Stansfield, 1974. ^nPelclova, 2003. ^oPfau, 2005. ^pPernis, 1965; Turner-Warwick, 1970; Stansfield, 1974; Lange, 1974. ^qZone, 1985; Zerva, 1989. ^rWhite, 1974. ^svan Bommel, 2009; Vaglio, 2009; Uibu, 2004; Sauni, 1998; Maguire, 1991. ^tcottin, 2008.
et al., 1974), but others demonstrated no association (Zone & Rom, 1985; Zerva et al., 1989; Pfau et al., 2005). There are undoubtedly differences in serum dilutions and technical approaches that may explain these differences. A more specific early detection marker for RA, antibodies to cyclic citrullinated proteins (anti-CCP), may help clarify this. However, the only known study of these autoantibodies in an asbestos-exposed population showed no increase in anti-CCP compared to controls (Pfau et al., 2008).

Some of these same studies did show an increase in ANA frequency with asbestos exposure, and despite technical disparities, small study sizes, and limited exposure assessments, the combined strength of these studies is compelling (Turner-Warwick & Parkes, 1970; Stansfield & Edge, 1974; Zerva et al., 1989; Pfau et al., 2005; Tamura et al. 1993; Nigam et al. 1993). Only one study indicated no association of positive ANA tests with asbestos exposure, but that study only consisted of 25 asbestos workers (Zone & Rom, 1985), and other immunological indices were positive, such as increased serum IgG/IgA and immune complexes. An interesting component of some of these studies is the evaluation of lung disease in ANA-positive patients, hypothesizing that the antibodies might play a role in fibrosis. In all these cases, positive ANA was associated with either more severe or more rapid progression of lung disease (Pfau et al., 2005; Gregor et al., 1979; Tamura et al., 1996; Turner-Warwick, 1973). Further study is needed, especially looking at different forms of asbestos. One study found an association of ANA seroconversion with only interstitial fibrosis, and another found an association only with pleural plaques (Tamura et al., 1996; Zerva et al., 1989). The former was a study of chrysotile exposure, and the latter was tremolite.

Only a couple of studies have attempted to identify specific targets for the ANA, and a commonality is the presence of anti-dsDNA (Pfau et al., 2005; Marczynski et al., 1994). Pfau et al. (2009) hypothesized that further study of the specificity of the autoantibodies might prove extremely informative in terms of mechanism of action, as well as diagnosis and progression. Antibodies to neutrophils (ANCA) were associated with silica and asbestos exposure, respectively (Pelclova et al., 2003). However, Pfau et al. (2005) did not find an association in their asbestos-exposed cohort.

Systemic autoimmune disease Similar to serological measurements, epidemiological reports of asbestos-exposed cohorts tended to be fairly small and suffer from problems with exposure assessment. However, the combined impact of these studies builds a fairly strong case for systemic autoimmune/rheumatological pathologies associated with asbestos exposure of various fiber types. Most frequently reported are associations with rheumatoid arthritis (Olsson et al., 2004; Greaves, 1979; White et al., 1974; Noonan et al., 2006). Other SAID are so rare that a study population would have to include nearly 100,000 subjects in order to have statistical strength. A recent examination of self-reported lupus or scleroderma patients showed associations with asbestos exposure based on extrapolations from a relatively small population (Noonan et al., 2006). Nevertheless, this account found a marked increase in the frequency of these two diseases above what would be expected in a population of that size (less than 10,000), illustrating the need for further assessment. A death certificate study described an increased risk for SSc deaths among persons having occupations with likely exposure to asbestos (Gold et al., 2007). Asbestos exposure was characterized using a job exposure matrix developed by an industrial hygienist. Interestingly, Gold et al. (2007) reported no increased risk for RA or SLE mortality associated with asbestos exposure, but it is possible that these two diseases are not often given as cause of death and therefore are not in the mortality statistics. There has also been some evidence of an association with ANCA-associated vasculitis (Stratta et al., 2001; Rihova et al., 2005; Inoue et al., 2004). This link may be underreported, since a primary symptom of this disease is interstitial pneumonias, which can be mistaken for asbestosis.
One of the strongest associations, based on literature review, is between asbestos exposure and periaortitis and retroperitoneal fibrosis, both of which are considered autoimmune diseases (van Bommel et al., 2009; Vaglio, 2009; Uibu et al., 2004; Sauni et al., 1998; Maguire et al., 1991; Boulard et al., 1995). This pathology is of interest due to the fiber burden of tissues in this area of the body following asbestos exposure (Uibu et al., 2009). Finally, it may be important to note that among rescue and recovery workers following the World Trade Center disaster, a higher than expected incidence of sarcoid-like disease has been reported (Izbicki et al., 2007). These personnel may have been exposed to asbestos during the rescue and recovery effort, but asbestos was identified as only one among hundreds of toxicants in the World Trade Center dust. In addition, although sarcoidosis is a multisystem disease that is mediated through inflammatory mechanisms that might place it under a broad definition of SAIDs, there is not general agreement that sarcoidosis should be considered an autoimmune disease. As the persons exposed to World Trade Center dust continue to be followed over time, the exact nature of ensuing pathologies may become clearer, but it will be difficult to associate such outcomes with specific exposure to asbestos in view of the complex mixture of dusts.

**Animal Studies**

Animal studies of asbestos and autoimmunity are extremely limited. A murine model of asbestos-induced autoimmunity was recently established by Pfau et al. (2008). Asbestos-exposed C57Bl/6 mice developed positive ANA tests and mild glomerulonephritis suggestive of an SLE-like disease. These common laboratory mice are not generally considered autoimmune prone, so this pathology occurred in the absence of a clear genetic predisposition for a particular disease process. Interestingly, the murine SLE-like disease was characterized by the production of autoantibodies that recognize dsDNA and Ro52, reminiscent of what was seen in the Libby asbestos exposures (Pfau et al., 2005). Therefore, the murine model of asbestos-induced autoimmunity appears to be both relevant and useful to study the immunological effects of amphibole asbestos. Such studies are critical to discovery of mechanism of action. For example, the possibility that autoantigens become antigenic due to proteolytic degradation or apoptotic processes was postulated. During cell stress or death, Ro52 undergoes intracellular translocation and was found to accumulate in apoptotic blebs during programmed cell death induced by a variety of oxidant challenges including asbestos. One study in fact showed that autoantibodies from asbestos-exposed mice bind to apoptotic blebs in which Ro52 is accumulated (Blake et al., 2008). In contrast to actual laboratory animal studies of autoimmunity, more investigations were conducted in animals to explore the general immune effects of asbestos, described below.

**In Vitro/Ex Vivo Immune Cell Studies**

Many early studies showed decreased cell-mediated immunity in vitro and in vivo following asbestos exposure, supporting the hypothesis that asbestos is not only carcinogenic, but also immunotoxic such that there is inadequate immunity against the tumors that arise. A few key papers are representative of a huge literature base (Kagan et al., 1977; Kagan, 1981; Lew et al., 1986; Manning et al., 1991; Miura et al., 2008). However, this is not really related to systemic autoimmunity, since the SAID are for the most part humoral. In fact, reduction of cell-mediated immunity may indirectly enhance humoral immunity, depending on the cellular/molecular mechanism. However, among these studies are at least two that provide evidence that silica produces cellular events that are more likely to produce autoimmune effects, whereas asbestos leads to effects that may promote cancer by reducing anti-tumor immunity (Nishimura et al., 2006; Wu et al., 2005; Ueki et al., 1994). This may help explain the stronger association of autoimmune disease with silica than asbestos, and further comparative studies are warranted.
For what would be considered nonpulmonary disease such as SAID, however, there are studies that explore what might be called the “adjuvant” effect of asbestos. There are excellent reviews exploring the immunological effects of asbestos and attempting to link the various pathologies via a unified immune dysregulation (Rom et al., 1991; Jagirdar et al., 1997). Recent studies describe activation of “inflammasomes” by asbestos and driving pro-inflammatory effects such as IL-1β secretion (Dostert et al., 2008). The inflammasome approach may help explain the extremely diverse effects of asbestos in surface markers and cytokines that were reported over the years (Miura et al., 2008; Wu et al., 2005; Ilavská et al., 2005; Perkins et al., 1993; Holian et al., 1997; Ottsuka et al., 2007; Hannant et al., 1985; Kinugawa et al., 1992; Thomas et al., 1994). One of the recurring ideas in both silica and asbestos immunotoxicology is that there are two events that occur to perpetuate autoimmune responses. The first is apoptosis, particularly of phagocytic cells such as the alveolar macrophage, leading to accumulating cellular debris. The second is immune activation via the “adjuvant” or inflammasome-activating effects, which would drive antigen presentation in an environment that is no longer tolerant of the insult. Despite the appeal of this theory, the literature thus far supports association, but not necessarily causation (Holian et al., 1997; Blake et al., 2008).

**Summary**

The limited number and scope of epidemiological studies that have explored a causal association between asbestos exposure and autoimmune disease make it difficult to draw conclusions (see Table 2). First, as with most studies of asbestos, the observations just described are focused primarily on male, occupationally exposed populations. This could be a limitation when evaluating clinical outcomes such as autoimmune disease that are more prevalent among women. The Libby study is unique in that it includes a substantial number of women with autoimmune disease who were environmentally exposed to asbestos (Noonan et al., 2006). Second, these studies are retrospective ones, which have limitations not only in terms of exposure assessment but also in terms of clarifying the temporal relationship between exposure, autoimmune response, and pulmonary manifestations of disease. Few of these studies used an appropriate age-matched comparison group. The quality of exposure assessment varied among these studies, with likely differences in the asbestos exposure classification. Serological analyses changed considerably over time, with earlier studies relying on tissue substrates for the studies while the current standard used in the more recent studies is HEP2 indirect immunofluorescence assay.

Nevertheless, from the combined studies the following were concluded:

- The frequency of positive ANA among asbestos-exposed individuals is higher than what would be observed among the general population.
- There appears to be a higher-than-expected risk of systemic autoimmune disease among asbestos-exposed populations.

The following are specific areas that need further study:

- Definition of an asbestos-associated autoimmune clinical entity (human mostly, but also animal for modeling and mechanisms of action).
- Temporal association between exposure and autoantibodies, and between autoantibodies and pulmonary disease (animal and human).
- Comparison of cellular/immune effects of different fiber sizes and types (animal and in vitro, human if possible).
- Specific autoantibody targets (animal and human).

**GASTROINTESTINAL EFFECTS OF ASBESTOS**

Asbestos-induced gastrointestinal tract (GIT) cancer would appear to have a
complicated etiology—dependent on the route, type, and duration of exposure. Environmental exposure through drinking water from cement pipelines containing chrysotile asbestos is the most obvious source for GIT exposure. However, inadvertent “swallowing” during occupational exposures and systemic deliverance following inhalation are also potential sources.

**Epidemiological Evidence**

Stomach cancer is the most consistently reported outcome of GIT-related pathologies due to asbestos exposure (Kjaerheim et al., 2005; Kanarek et al., 1980; Polissar et al., 1983; Andersen et al., 1993; Hillerdal, 1980). However, there are reports of increased colon (Kjaerheim et al., 2005; Germani et al., 1999) and esophageal cancer (Kang et al., 1997) in response to asbestos. In contrast, additional studies evaluating environmental exposure to asbestos via the drinking water noted no increased disease of the GIT on the whole, including stomach cancer (Harrington et al., 1978; Levy et al., 1976; Browne et al., 2005; Hodgson & Jones, 1986; Toft & Meek, 1983). It is possible that discrepancies in the conclusion of these studies might be due to differences in the integrity of the asbestos pipelines and therefore degree of exposure. In addition, mineral composition of the water likely affects toxicity of the asbestos. Studies examining differences in the toxic properties of asbestos found that it may be modulated by changing the asbestos surface chemistry, specifically Fe oxidation potential (Chio et al., 1994). Furthermore, presoaking asbestos fibers with the Fe chelator deferoxamine diminishes toxicity in vitro (Weitzman et al., 1988; Goodglick & Kane, 1986, 1990; Goodglick et al., 1989), and modifying the surface of asbestos with metal oxides reduces the hemolytic potential of chrysotile, amosite, and crocidolite in sheep erythrocytes (Hahon et al., 1986).

The effects of occupational asbestos exposure on GIT cancers have also been examined in a number of studies. Occupational exposures are generally higher than would be expected from an environmental exposure and include both inhalation and inadvertent ingestion of asbestos fibers. The evidence linking occupational exposure to stomach cancer is more convincing than studies examining exposure through the drinking water and appears to be primarily due to chrysotile or crocidolite asbestos (Lumley, 1976; Raffn et al., 1989; Newhouse et al., 1988; Armstrong et al., 1988; Botha et al., 1986; Szeszenia-Dabrowska et al., 1998; Sun et al., 2008; Enterline et al., 1987). Again, studies focusing on the GIT as a whole report little evidence to suggest a relationship even when the exposure is occupational in nature (Berry & Newhouse, 1983; Churg & Warnock, 1979; Reid et al., 2004; Thomas et al., 1982; de Klerk et al., 1989; Pira et al., 2009; Albin et al., 1990; Gardner et al., 1986; Finkelstein, 1989; Hodgson & Jones, 1986; Tsai et al., 1996). In fact, studies finding a link between occupational asbestos and general GIT cancers are few compared to studies looking at specific endpoints, such as stomach cancer (Weiss, 1977; Lacquet et al., 1980; Finkelstein, 1984). Finally, a literature search for a relationship between asbestos and inflammatory bowel diseases resulted in only one suggestive report. In this case study, a pipefitter with known asbestos exposure and Crohn’s disease later developed cancer of the small bowel (Lashner, 1992). However, given the inflammatory nature of asbestos-related pulmonary diseases, the issue warrants consideration.

**Type and Route of Exposure**

Differences in the carcinogenic potential of different asbestos fibers are not as yet clear as it relates to GIT disorders. There does, however, appear to be more evidence linking the chrysotile form to diseases of the GIT as opposed to crocidolite.

The most likely route of exposure for GIT disorders due to asbestos is in contaminated drinking water. Millette et al. (1983) estimated that the majority of water consumers are exposed to less than 1 million fibers/L, but some populations could be exposed to greater than 10 million fibers/L. In fact, the California aqueduct system has been reported to contain billions of fibers per liter as measured by three
separate filtration processes followed by TEM (McGuire et al., 1982). In addition, water samples analyzed via electron microscopy (EM) revealed that the distribution of fiber size in the water is dependent on its source. Asbestos cement pipelines result in mean fiber lengths of 4 μm and asbestos due to natural erosion results in an average of 1-μm fiber pieces (Millette et al., 1980). Furthermore, contaminated food supplies must also be considered as a possible source (Rowe, 1983). It is important to note that early methods for detection of asbestos fibers (including EM protocols) lacked the ability to determine a statistically relevant number of the long fibers having the greatest hazard potential (Lippmann, 1994).

An important consideration regarding GIT exposure is transport and retention of fibers, since the GIT has large volume transport and export that could eliminate the fibers fairly rapidly. No studies were found examining the export of asbestos from the GIT.

**Animal Studies**

Early attempts to discern mechanisms underlying the carcinogenic potential of asbestos fibers show that ingestion of UICC standard chrysotile A (5 mg/kg for 2 wk) resulted in an increase in DNA synthesis in the small intestine and colon of the rat (Amacher et al., 1974). In addition, a rise in the incorporation of \(^{3}H\)thymidine into DNA following ingestion of 50 mg/day for 1 wk was observed (Jacobs et al., 1978). Glandular stomach cancer was induced in rats by intra-abdominal insertion of a pouch containing 100 mg chrysotile and beef fat (Kogan et al., 1987). Furthermore, both crocidolite- and chrysotile-gavaged rats (3 treatments of 33 mg/kg each) showed induction of aberrant crypt foci, which is indicative of colon carcinogenesis (Corpet et al., 1993). Additional studies noted cellular debris and Alcian blue staining in the ileum, rectum, and colon along with mucosal changes in the ileum 14 mo after ingestion of 50 mg/day chrysotile asbestos (Jacobs et al., 1978). Moreover, chrysotile ingested long term via the drinking water (0.5 g/L) in rats suggests that absorption of nonmetabolizable sugars from the GIT is adversely affected (Delahunty & Hollander, 1987). However, in Syrian golden hamsters given amosite or short- or intermediate-range chrysotile in the diet (at a concentration of 1% of pelleted diet) for their lifetime, no increases in neoplasms were seen for either fiber type (McConnell et al., 1983). In addition, the complete set of National Toxicology Program (NTP) feed studies provided no convincing evidence of GI neoplasms overall (NTP, 1985, 1988, 1990).

**In Vitro Studies**

Few in vitro studies were conducted using cells derived from the GIT system. However, it is known that asbestos fibers penetrate epithelial cells of both the pulmonary and GIT systems (Mossman, 1983). In addition, the variable effects of asbestos on GIT epithelium exposed to asbestos are likely a result of differences in surface charge, crystallization, and dimensional characteristics (Mossman, 1983).

**Summary**

The GIT effects produced by asbestos exposure appear to be minimal, but data are inconclusive at best. The most likely result of exposure to asbestos, either environmentally or through occupational hazards, is development of stomach cancer. Chrysotile appears to pose a greater threat than crocidolite. However, IARC recently concluded the evidence to support asbestos-induced stomach cancer to be “limited” (Straif et al., 2009). There is a great deal of inconsistency in the studies of the GIT effects of asbestos, making it difficult to come to any strong conclusions (see Table 3).

However, in summary the following were concluded:

- The GIT effects of asbestos are relatively infrequent as compared to the pulmonary and peritoneal effects; however, there remains the possibility for a link to stomach cancer.
- The studies on asbestos in drinking water and from food sources are inconclusive.
TABLE 3. Publications on Asbestos-Induced Gastrointestinal Disease

| Endpoint                     | Fiber type (if known) | Occupational exposure | Ingested/water | Animal studies |
|------------------------------|-----------------------|-----------------------|----------------|----------------|
| GI cancer (general)          | Chrysotile            | 6(–)                  | 1(–)           | 1(+)^d         |
|                              | Crocidolite           | 2(+)^b                 |                |                |
|                              | Unknown               | 1(–)^c                 |                |                |
|                              | Amosite or Tremolite  | 5(+)^f                 | 3(–)^h         |                |
|                              |                       |                       |                |                |
| Colon/colorectal cancer      | Chrysotile            | 3(+)                  | 1(+)^k         | 3(+)          |
|                              | Crocidolite           | 1(–)                  |                | 1(+)^m         |
|                              |                       |                       |                |                |
| Stomach cancer               | Unknown               | 4(+)                  | 2(+)^o         |                |
|                              | Crocidolite           | 3(+)^p                 |                |                |
|                              |                       | 1(–)^q                 |                |                |
|                              | Chrysotile            | 2(+)                  |                |                |

Note. The number indicates how many articles were found with a positive (+) or negative (–) association between asbestos and disease. “Unknown” exposures indicate the data came from occupational exposure matrices, including textiles, insulation, or cement workers.

Sources: aBerry, 1983; Thomas, 1982; Pira, 2009; Albin, 1990; Gardner, 1986; Finkelstein, 1989. bFinkelstein, 1984; Weiss, 1977. cToft, 1983. dJacobs, 1978a. eReid, 2004. fKang, 1997; Lumley, 1976; Lacquet, 1980; Newhouse, 1985; Selikoff, 1974. gHodgson, 1986; Tsai, 1996. hBrowne, 2005; Harrington, 1978; Levy, 1976. iMcConnell, 1983a, 1983b. jGermani, 1999; Albin, 1990; Szeszenia-Dabrowska, 1998. kKjaerheim, 2005. lCorpet, 1993; Amacher, 1974; Donham, 1980. mCorpet, 1993. nLumley, 1976; Sun, 2008; Enterline, 1987; Raffn, 1989. oKjaerheim, 2005; Andersen, 1993. pNewhouse, 1988; Armstrong, 1988; Botha, 1986. qde Klerk, 1989a. rKanarek, 1980; Polissar, 1983.

The following are areas that need further study:

- It would be helpful if studies evaluating cohorts exposed through drinking water examined the mineral content of the water.
- Additional animal studies evaluating the GIT effects of orally administered asbestos with different mineral content (i.e., Fe, nickel, etc.).
- Additional animal studies examining the GIT affects following inhalation exposure.
- Additional studies examining rate of fiber passage versus retention in the GIT tract following ingestion.

REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF ASBESTOS

The reproductive effects of asbestos are poorly understood but include ovarian cancer and possibly an increase in the occurrence of stillborn babies and infant mortality as well as childhood mesothelioma. While there are case studies describing intratesticular malignant mesothelioma in relation to asbestos (Attanoos & Gibbs, 2000), it is an extremely rare and poorly characterized disease. In addition, there is limited epidemiological evidence showing an increased odds ratio (OR) for cancer of the testes following asbestos exposure (Polissar et al., 1982).

Adverse effects to the reproductive system were first considered following passive observations of an elevated rate of ovarian cancer in cohorts of asbestos exposure. In fact, early reports linking asbestos with ovarian cancer include a report of 9 out of 23 women with asbestosis dying of abdominal neoplasms thought to be of ovarian origin (Keal, 1960). More recently, evidence using electron microscopy (EM) showed that transplacental transfer of asbestos fibers occurs (Haque et al., 1992). This led to studies on the effects of prenatal exposure to asbestos.

Epidemiological Evidence

Epidemiological evidence supporting an increased incidence of ovarian cancer due to asbestos exposure has been a matter of debate. There are a number of suggestive studies; however, most of these reports fail to
reach statistical significance. In addition, the potential for misdiagnosis of primary diffuse malignant peritoneal mesothelioma in women further complicates the issue (Kerrigan et al., 2002), particularly in older studies that did not use specific markers directed toward serous ovarian carcinoma (Bollinger et al., 1989). Nevertheless, IARC recently concluded that the evidence to date is sufficient to consider asbestos an ovarian carcinogen (Straif et al., 2009). Studies include a cohort of East London factory workers from 1933–1980 who reportedly elevated rates of ovarian cancer (Newhouse et al., 1985 and a confirmation of excessive ovarian cancer in female gas mask assemblers during World War II (Wignall & Fox, 1982; Acheson et al., 1982). Furthermore, in a study of Italian women compensated for asbestosis, an increase in ovarian cancer was reported (Germani et al., 1999) and more recently in Italian cement workers (Magnani et al., 2008). Other studies demonstrated increased OR for ovarian cancer in exposed women include a cohort of Australian blue asbestos workers (Reid et al., 2009), Italian textile workers (Pira et al., 2005), and female Norwegian pulp workers (Langseth & Kjaerheim, 2004). Again, while the findings in the studies listed here did not always reach significance, taken together they provide noteworthy evidence of a link between asbestos exposure and ovarian cancer.

In addition to ovarian cancer, asbestos may exert adverse effects on other aspects of the reproductive system. Transplacental transfer of asbestos was first considered following the observation that mesothelioma in children has a shorter latency period than is common in adults following asbestos exposure (Wassermann et al., 1980). Transplacental transfer is further supported by evidence that when the exposure can be traced to early in childhood, the latency period remained similar to that seen in adults (21–25 yr) (Wassermann et al., 1980) (for additional information see Testa et al., this issue). Furthermore, this implies the possibility that prenatal exposure may result in highly malignant cases of mesothelioma in children.

In addition to an increased risk of childhood mesothelioma, there is some evidence suggesting that transplacental transfer of asbestos results in elevated frequency of infertility, stillbirth, and infant mortality. Specifically, a rise in the number of stillborn babies was reported in women working in Russian asbestos factories (Tsurikova et al., 1992). Haque et al. (1992) used EM to examine the lungs, liver, and placenta from five stillborn infants. An asbestos fiber burden ranging from 71,000 to 357,000 fibers/g wet weight was detected in at least one organ of all five infants (Haque et al., 1992). Haque et al. (1996) continued by examining the organs from 40 stillborn infants and comparing them to the placenta from liveborn controls. Tissue digests were characterized as to the type of asbestos using EDXA-EM and selected-area diffraction analysis. Small, thin, uncoated asbestos fibers were found in 15 of the 40 stillborn infants, while no fibers were found in the placental tissue of any live-born controls (Haque et al., 1996). Interestingly, in a larger third study by Haque et al. (1998) using the same methods, low numbers of asbestos fibers were also found in 15% of the live-born placental controls. This suggests that there is a threshold for prenatal exposure that is lethal to the fetus, but again raises the possibility that the surviving infants have a higher risk for developing childhood mesothelioma.

Type and Route of Exposure

In studies on Chinese hamster ovary cells, UICC chrysotile fiber type B was shown to exert a greater toxicity than either UICC crocidolite or amosite (Neugut et al., 1978), suggesting that chrysotile is more likely to produce adverse reproductive effects. However, there is little work that has been done to support this assumption.

There have been few studies exploring the route of exposure for asbestos-induced ovarian cancer, probably because most epidemiological studies focus on occupationally exposed men. However, using analytic EM, asbestos was detected in the ovary and Fallopian tubes
of women with known contact (Heller et al., 1999). In a study of Norwegian pulp workers who were diagnosed with ovarian cancer, fibers were found in the ovaries of two women with possible secondary exposure from a spouse also employed in the industry (Langseth et al., 2007). In addition, a significant asbestos burden was found using analytic EM in the ovaries of women with no documented exposure other than being married to an asbestos worker (Heller et al., 1996). It is known from early studies that carbon particles injected into the vaginal space of women while under anesthesia were detected in the Fallopian tubes within a few hours (Egli & Newton, 1961). Therefore, likely routes of contact include traditionally defined occupational exposure (inhalation and ingestion) as well as possible secondary exposure during coitus.

Prenatal asbestos exposure might occur following any type of contact that would result in systemic distribution of the fibers and allow for transplacental transfer to occur. This would include occupational (inhalation), as well as environmental exposures.

**Animal Studies**

There are few studies measuring the effects of asbestos on reproduction in vivo. However, ip injection of asbestos in guinea pigs and rabbits resulted in changes in ovarian epithelial cells similar to that seen in the early stages of ovarian cancer (Graham & Graham, 1967). Furthermore, Schneider and Maurer (1977) observed a decrease in postimplantation survival of embryos in pregnant CD-1 mice given chrysotile asbestos in their drinking water.

It was also demonstrated through the use of EDXA-EM analysis that asbestos is transferred to the fetus through the placenta in pregnant mice given an iv dose of asbestos (Haque & Vrazel, 1998), and transplacental transfer of chrysotile asbestos was also found in rats (Vanchugova et al., 2008). In addition, oral administration of chrysotile asbestos to pregnant mice resulted in fibers detected in the lung and liver of pups by EDXA-EM (Haque et al., 2001).

**In Vitro Studies**

Mechanisms of asbestos-induced ovarian cancer and infertility are poorly understood. However, a cell-mediated immunity towards primary rat fetal cells from rats with Canadian chrysotile B fiber-induced mesothelioma was observed (Stevens et al., 1983), suggesting a link between fetal death and the immune system. In addition, a decrease in surface labeling of glycolipids and glycoproteins in hamster embryos treated with chrysotile asbestos was noted (Saat et al., 1980), along with a rise in micronucleated human amniotic cells (Dopp et al., 1997). Furthermore, incubation of rat embryo cells with crocidolite for 2–48 h resulted in an increase in DNA strand breakage within 2–6 h (Libbus et al., 1989).

**Summary**

Overall, there has been little work on the reproductive consequences of asbestos (see Table 4). However, there is sufficient evidence to draw concern and warrant further investigation. Particularly, more studies are required to solidify the concerns regarding asbestos and ovarian cancer. In addition, effects on fertility and the developing fetus need to be closely examined.

In summary, the following broad possibilities regarding the reproductive effects of asbestos were concluded:

- High levels of asbestos exposure has a high probability of resulting in ovarian cancer.
- Women who have occupational exposure and who also live with someone who works with asbestos have the highest risk for ovarian cancer.
- While there are case reports of asbestos-related testicular mesothelioma, it is an extremely rare disease.
- Evidence suggests transplacental transfer of asbestos can occur.
- Transplacental transfer of asbestos may result in an increase in stillborn infants.
- At low levels of prenatal asbestos exposure there is the possibility of increased childhood mesothelioma.
TABLE 4. Publications on Asbestos-Induced Reproductive Disease/Disorders

| Endpoint                      | Fiber type                     | Primary route of exposure | Human studies | Animal studies | In vitro |
|-------------------------------|-------------------------------|----------------------------|---------------|----------------|---------|
| Infant mortality/stillbirths  | Chrysotile                    | Transplacental             | 4(+)         | 1(+)          | 3(+)    |
| Decreased fertility           | Chrysotile                    | Ingested                   | 1(+)         |                |         |
| Ovarian cancer                | Chrysotile and/or crocidolite | Occupational              | 9(+)         | 1(+)          |         |
| Tumors of the testis          | Unknown, case studies         | Occupational              | 1(+)         |                |         |
| Intratesticular mesothelioma  | Unknown                       | Drinking water             | 1(+)         |                |         |

Note. The number indicates how many articles were found with a positive (+) or negative (−) association between asbestos and disease. “Unknown” exposures indicate the data came from occupational exposure matrices, including textiles, insulation, or cement workers. Sources: aHaque, 1992; 1996; 1998; Tsurikova, 1992. bHaque, 2001. cSchneider, 1977. dSaat, 1980; Dopp, 1997; Stevens, 1983. eGermani, 1999; Langseth, 2004; Magnani, 2008; Pira, 2005; Reid, 2009; Acheson, 1982; Newhouse, 1985; Wignall, 1982; Berry, 2000. fMillette, 1983. gGraham, 1967. hAttanoos, 2000. iPolissar, 1982.

The following are areas that need further study:

- Animal studies examining the link between asbestos and ovarian cancer are needed to further clarify the strength of the association.
- Prenatal exposure and childhood mesothelioma is little more than a hypothesis at this point; therefore, epidemiological and animal studies would provide a large degree of insight.
- Infertility due to asbestos exposure is a definite possibility, and has been poorly studied at this point.
- Increased stillborn and infant mortality due to prenatal asbestos exposure should be further examined.

**MISCELLANEOUS EFFECTS OF ASBESTOS**

The possibility of other asbestos-induced health effects does exist. These include brain-related tumors, blood disorders due to the mutagenic and hemolytic properties of asbestos, and peritoneal fibrosis—although this has only been documented in animals. In addition, the cocarcinogenic potential of asbestos needs to be considered as a possible health threat.

However, studies reporting a positive association include an increase in the number of deaths due to brain tumors observed in petrochemical workers exposed to asbestos in the United States and Canada (Seidman et al., 1982) and rock salt workers in Italy (Tarchi et al., 1994). In addition, there are a number of cases of malignant brain tumor metas- tases from pleural mesothelioma (Kawai et al., 1997; Wronski & Burt, 1993; Falconieri et al., 1991).

In addition to brain tumors, there is some evidence linking blood-related disorders to asbestos. Evidence includes an increase in the number of double-stranded DNA breaks in white blood cells from workers with an occupational exposure to crocidolite (Marczynski et al., 1994). Furthermore, when human peripheral blood lymphocytes were incubated with chrysotile, an inhibition of blastoid transformation and beta-2 microglobulin production was observed (Nakatani, 1983). Additional reports have shown a rise in the concentration of 8-hydroxy 2’-deoxyguanosine adducts in the DNA from the blood of highly exposed workers (Marczynski et al., 2000).

**Epidemiology Studies**

There is little evidence to link asbestos exposure with a rise in brain-related tumors. However, studies reporting a positive association include an increase in the number of deaths due to brain tumors observed in petrochemical workers exposed to asbestos in the United States and Canada (Seidman et al., 1982) and rock salt workers in Italy (Tarchi et al., 1994). In addition, there are a number of cases of malignant brain tumor metastases from pleural mesothelioma (Kawai et al., 1997; Wronski & Burt, 1993; Falconieri et al., 1991).

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**Animal Studies**

Evidence of blood-related pathologies due to asbestos exposure exist in animal studies, although it is unknown whether the effect is direct or a consequence of increased inflammation. Nevertheless, chrysotile was found to be highly hemolytic to rat erythrocytes (Nadeau
et al., 1987) as well as to red blood cells in humans, rats, and sheep (Pele & Calvert, 1983). Oxidative stress was suggested to play an important role in these pathologies using common methods to measure markers of reactive oxygen species. Specifically, analysis of red blood cells from rats 30 d following a single intratracheal exposure to either chrysotile or crocidolite revealed an elevation in lipid peroxidation as measured by thiobarbituric acid-reactive substances (TBARS) activity, as well as decreased total glutathione and ascorbic acid levels (Afaq et al., 1998). In addition, increases in malondialdehyde, an end-product of lipid peroxidation, were measured in response to crocidolite treatment in human peripheral blood-derived neutrophils, guinea pig peritoneal macrophages, and guinea pig alveolar lung lavage cells (Yano, 1988).

A link between asbestos and peritoneal fibrosis is supported by studies utilizing mice as models for fibrogenesis. These reports showed a rise in events leading to initiation of a fibrogenic response in the mouse peritoneum following delivery of chrysotile using a sealed diffusion chamber (Bateman et al., 1982) or injected directly into the peritoneal cavity (Wirth, 1975). In addition, medium from rat peritoneal macrophages incubated with asbestos released fibrogenic factors in rat fibroblasts (Aalto & Heppleston, 1984).

**In Vitro Studies**

In vitro systems were used to study the cocarcinogenic effects of asbestos as well as looking at potential mechanistic pathways. For example, benzo[a]pyrene (BaP), a common carcinogen resulting from incomplete combustion of organic materials (including common foods) (Le Marchand et al., 2002), was found to increase mutagenicity when given concomitantly with asbestos to rat liver epithelial cells (Reiss et al., 1983). Perhaps the fibers act as cocarcinogens by allowing adsorbed contaminants access to the cell. This is supported by evidence that chrysotile enhances the uptake of BaP in rat liver microsomes (Lakowicz & Bevan, 1980). In addition, chrysotile was found to reduce the ability of the cells to metabolize BaP (Kandaswami & O’Brien, 1983). Kandaswami et al. (1986) suggested that these phenomena are due to chrysotile’s ability to inhibit critical microsomal enzymes such as aryl hydrocarbon hydroxylase, aminopyrine N-demethylase, and dimethylnitrosamine demethylase. Furthermore, when crocidolite treated with BaP was given to rats in the drinking water, DNA strand breaks were potentiated (Varga et al., 1999), and chrysotile administered alone to rat liver epithelial cells is a potent inducer of binucleation (Pelin et al., 1995).

Mechanistic studies demonstrated an increase in lipid peroxidation in rat liver microsomes treated with either crocidolite or chrysotile (Fontecave et al., 1987; Gulumian et al., 1983), suggesting that oxidative stress may also play a role in the toxicity of asbestos. This is further supported by the ability of N-acetylcysteine to inhibit the gene expression of proliferin in the pluripotent C3H10T1/2 stem cell line following treatment with amosite, crocidolite, or chrysotile (Parfett et al., 1996). Moreover, phospholipase A(2) and phosphokinase C inhibitors prevented a chrysotile-induced increase in superoxide formation in murine peritoneal macrophages (Nakajima et al., 2000). When a noncellular system was used to test the ability of asbestos to generate the hydroxyl radical, crocidolite proved to have the greatest potency, followed by amosite and then chrysotile. This trend correlated well with pleural inoculations in rats (Maples & Johnson, 1992).

**NON-PULMONARY ENDPOINTS OF ASBESTOS EXPOSURE—HYPOTHESIS FOR MECHANISM OF ACTION**

In order for asbestos to produce nonpulmonary pathologies, at least one of the following must occur:

- Translocation of the fibers to nonpulmonary sites.
• Activation of systemic signaling (cytokines, immune activities, etc) that impacts nonpulmonary sites.
• Metastasis of primary lung or pleural tumors to nonpulmonary sites.

**Tissue Asbestos Burden and Translocation**

Research regarding the fiber movement and tissue burden of asbestos has been an important component to our current understanding of the effects of asbestos (see Table 5). In the lung it affects exposure assessment due to the tendency of asbestos to bioaccumulate. In nonpulmonary systems, the issue is significant due to the potential for translocation to other tissues. The majority of reported cases of asbestos exposure are occupational in nature. However, other pathways include contaminated food and water sources, as well as secondary exposures due to contact with someone who has been occupationally exposed.

Unfortunately, there are inherent difficulties in the study of fiber distribution, particularly regarding detection and quantification of the fibers. Historically, detection depended on light microscopy visualization of asbestos bodies or ferruginous bodies. This method has innate shortcomings due to difficulty in finding the appropriate orientation of the sample. However, light microscopy is reportedly dependable for detection of fibers larger than 0.3 μm in width. More accurate detection of thinner fibers requires electron microscopy (Dodson et al., 2007). Most of the more current literature used multiple detection techniques to maximize confidence in the data.

**Tissue burden** Occupational asbestos exposure is primarily via the lungs with a secondary exposure to the GIT through inadvertent swallowing of the fibers. There is increasing evidence for systemic exposure following inhalation of asbestos fibers, allowing for the possibility of asbestos contact with distal tissues. For example, chrysotile fibers were detected by TEM in the urine of workers in a factory producing roof tiles (Finn & Hallenbeck, 1984), and by LM in the

### Table 5. Publications on Asbestos Tissue Burden/Translocation

| Tissue                        | Disease outcome | Fiber type | Exposure            | Human | Animal |
|-------------------------------|-----------------|------------|---------------------|-------|--------|
| Lymph nodes, lung draining    | Asbestosis or lung cancer | Amphibole Chrysolite | Occupational | 3(+)^a |        |
| Lymph nodes, thoracic         | Unknown         | Short, noncommercial amphiboles | Nonoccupational (environmt) | 1(+)^b |        |
| Lymph nodes, thoracic         | Pleural meso    | Crocidolite | Cigarette filters   | 1(+)^c |        |
| Lymph nodes, para-aortic/mesen | Asbestos-related lung disease | Mixed amph/chrys | Low-level occupational | 1(+)^d |        |
| Liver                         | See note e      | Mixed      | Pulmonary or gavage | 3(+)^e | 1(+)f |
| Spleen                        | See note e      | Mixed      | Pulmonary or gavage | 2(+)^g | 2(+)^i |
| Colon                         | Colon carcinoma | Amosite and chrysotile | Occupational | 2(+)^j |        |
| Kidney                        | Lung cancer or meso | Crocidolite | Occupational or gavage | 3(+)^k | 1(+)l |
| Ovary                         | Risk for ovarian cancer? | Crocidolite and chrysotile | Household contact | 3(+)^m |        |
| Transplacental                | Stillborn       | “short, thin fibers” | Maternal (environmt) | 3(+)^n |        |
| Omentum, mesentery            | Risk of peritoneal mesothelioma? | Amphiboles and chrysotile | Various | 3(+)^o |        |
| Pancreas                      | Asbestosis      | Mixed      | Occupational or gavage | 1(+)p | 1(+)q |
| Heart                         | See note e      | Mixed      | Occupational or gavage | 1(+)r | 1(+)q |

Note. The number indicates how many articles were found with a positive (+) or negative (−) association between asbestos and outcomes. Sources: 1Doddson, 2007; 1990; Tossavainen, 1994. 2Doddson, 2000. 3Doddson, 2006. 4Uibu, 2009. 5Although no disease outcome was noted, fibers were detected in these studies. 6Watanabe, 1994; Kobayashi, 1987; Huang, 1988. 7Williams, 2001. 8Kobayashi, 1987; Watanabe, 1994. 9Kaczenski, 1984, Williams, 2001. 10Ehrlich, 1991; Huang, 1988. 11Watanabe, 1994; Kobayashi, 1987; Tossavainen, 1994. 12Patel-Mandlik, 1983. 13Heller, 1996; 1992; Langseth, 2004. 14Haque, 1996, 1992, 1998. 15Doddson, 2006; 2001; Heller, 1996. 16Huang, 1988. 17Kaczenski, 1984. 18Kobayashi, 1987.
extrapulmonary tissue from workers with occupational exposure (Langer, 1974). Asbestos burden evaluated in autopsied cases by EDXA-TEM also showed that extrapulmonary fibers increase as pulmonary values rise while the fiber type remains consistent (Huang et al., 1988). Furthermore, a lung asbestos burden of 0.45 million fibers/g dry tissue or greater as measured using EDXA-TEM has been useful in predicting fiber burden in the abdominal lymph nodes of individuals believed to have died from asbestos-related disease (Uibu et al., 2009).

Fiber Translocation Studies support widespread distribution of asbestos, starting with likely clearance from the lung (or peritoneum) via macrophages to the draining lymph nodes (Dodson et al., 1990, 1991, 2000, 2007) (for additional information see Mossman et al., this issue, and Aust et al., this issue.). In addition, evidence of lymphatic trafficking of the fibers comes from studies showing the presence of fibers in the spleen (Huang et al., 1988; Kobayashi et al., 1987; Williams et al., 2001), liver, and kidney (Huang et al., 1988; Kobayashi et al., 1987; Williams et al., 2001; Tossavainen et al., 1994). Due to the ability of asbestos to translocate from the lung to the rest of the body via pulmonary lymph and the blood stream, systemic exposure may be highly influenced by fluid dynamics of the exposed individual (Miserocchi et al., 2008). Further, it is likely that asbestos exposure results in an impaired barrier function of the lung. This is supported by a report that lung instillation of polyethylene glycol (PEG) polymers in rats along with crocidolite resulted in increased urinary recovery of >854-kD PEGs (Folkesson et al., 1993).

Animal Studies While most studies use human autopsy samples from asbestosis or asbestos-related cancer patients, a few studied fiber distribution following exposure in animals. Chrysotile delivered through the food supply results in fibers being detected in the kidneys (50 mg/kg dose, analyzed by TEM) (Patel-Mandlik & Millette, 1983), lungs (1.5–3.0 g/L dose, as indicated by the presence of asbestos bodies) (Hasanoglu et al., 2008), and bloodstream (Weinzweig & Richards, 1983) of rats and in the kidneys of baboons (measured using TEM) (Patel-Mandlik et al., 1979). In addition, fibers were detected by TEM in the stomach, heart, spleen, pancreas, and blood of baboons gavaged cumulatively with 800-mg doses of either chrysotile or crocidolite fibers (Kaczenski & Hallenbeck, 1984). In rats, asbestos fibers were found in the lymph 2–24 h following oral exposure with 50% of the total load absorbed within 6 h (Masse et al., 1980). In mice, studies on fiber content in tissue after ip instillation suggest the fibers penetrate rapidly (Winkler & Ruttner, 1982), whereas examination of the epithelial lining of the gut following ingestion of UICC chrysotile A or UICC crocidolite reportedly showed no evidence of penetration when examined by EM (Davis et al., 1974). Similarly, the amphibole amosite (UICC) did not appear to penetrate the GIT of rats when analyzed by LM after a daily dose of 100 mg for 5 d (Meek, 1983).

Summary Fiber distribution after a variety of asbestos exposures in both humans and animals provides evidence for widespread migration of the fibers to various organs. These data support the hypothesis that nonpulmonary effects of asbestos might be due to the presence of the fibers in those sites. Nevertheless, the literature does not rule out the possibility of a systemic effect that might enhance carcinogenesis and fibrosis in organs other than those directly impacted by asbestos exposure. The second and third hypotheses that asbestos may enhance extrapulmonary cancers as well as metastasis from primary pulmonary tumors merit consideration, but require further study. Large-scale prospective studies of different asbestos exposures are needed to more clearly understand the temporal and mechanistic relationships of cancer in nonpulmonary sites following asbestos exposure.
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