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ASBESTOS

MEDITEXT ® - Medical Management

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ASBESTOS

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3.0 CLINICAL EFFECTS

3.1 SUMMARY OF EXPOSURE

3.1.1 ACUTE EXPOSURE

- A. No well-documented fatalities have been reported as a result of acute exposure. Fulminant pulmonary asbestosis following massive short-term industrial exposure is now only of historical interest. Asbestos toxicity is usually manifested after a long latent period. The respiratory tract is the usual target organ. There are two main categories of asbestos diseases.
 - 1. Fibrosis/effusions of the lungs and pleura (asbestosis).
 - 2. Asbestos-related cancers, primarily mesothelioma of the pleura and peritoneum and bronchogenic carcinoma.
- B. Cor pulmonale is secondary to fibrosis and increased resistance to pulmonary capillary blood flow.
- C. Autoimmune disorders may be more common in patients with overt asbestosis.

3.1.2 CHRONIC EXPOSURE

- A. Signs and symptoms are rarely acute in onset. Pulmonary fibrosis or lung cancer are delayed effects.

3.4 HEENT

3.4.5 THROAT

- A. LARYNGEAL ASBESTOSIS - Hyperplastic chronic laryngitis was identified in 10 workers in an asbestos cement factory (Kambic et al, 1989). 3 of 4 tissue specimens examined by scanning electron microscopy had asbestos fibers on the epithelial surface.

3.5 CARDIOVASCULAR

3.5.1 ACUTE EFFECTS

- A. COR PULMONALE
 - 1. In patients with asbestosis, severe pulmonary fibrosis and pulmonary hypertension secondary to increased resistance to pulmonary capillary blood flow can cause compensatory hypertrophy of the right heart (ATSDR, 1990).
- B. PERICARDITIS
 - 1. Chronic constrictive pericarditis has been associated with asbestos exposure (Fischbein

et al, 1988; Davies et al, 1991).

3.6 RESPIRATORY

3.6.1 ACUTE EFFECTS

A. ASBESTOSIS

1. **DEFINITION** - Asbestosis is defined as an irreversible diffuse bilateral interstitial fibrosis primarily affecting the lower 2/3 of the lung (ATSDR, 1990; Newhouse, 1983). Either heavy exposure for a short time or lower-level exposure over a longer period may result in asbestosis; cases have resulted from intense exposure of one day's duration (ATSDR, 1990).
2. **CLINICAL MANIFESTATIONS** - Pleural asbestosis generally develops from chronic, low-level exposure; parenchymal asbestosis is related to higher-level exposures (ATSDR, 1990).
 - a. Signs and symptoms include dyspnea on exertion, finger clubbing, clicking, and rales (bilaterally in the posterior axillae) (ILO, 1983; Newhouse, 1983). Persistent pleuritic pain may be a manifestation of asbestos-induced pleural disease (Miller, 1990).
 - b. Cough is usually not present except in the late stages when distressing paroxysms occur (ILO, 1983). Increased sputum production is not present unless there is concomitant smoker's bronchitis (ILO, 1983).
 - c. Early x-rays may not be diagnostic (Newhouse, 1983; Talcott & Antman, 1988).
 - d. Clinical manifestations typically appear 10 to 40 years after onset of exposure (ATSDR, 1990; Demers et al, 1990). However, radiologic changes can occur before 20 years.
 - e. Signs, symptoms, and abnormalities increase with longer duration of exposure (Demers et al, 1990; Selikoff et al, 1990). The typical restrictive pulmonary dysfunction can be obscured by chronic obstructive pulmonary disease due to smoking (Mossman & Gee, 1989).
 - f. A long latency period of at least a decade exists between onset of histologic lesions and radiologically detectable stigmata (Kagan, 1988).
3. **CLINICAL COURSE** - Pleural thickening progresses at the greatest rate among crocidolite miners and millers who develop early thickening after exposure. This progression decreases with time so that no progression may be noted more than 15 years after onset (de Klerk et al, 1989).
 - a. Asbestosis may progress even after exposure terminates (Kagan, 1988; Talcott & Antman, 1988).
 - b. Although asbestosis progresses slowly and may cease at any time, death may occur from cor pulmonale or from lung cancer (Newhouse, 1983).
 - c. Progressive restrictive pleural fibrosis in a small proportion of patients can cause severe dyspnea, decreased vital capacity, total lung capacity, residual volume, and diffusing capacity, with eventual ventilatory failure and death (Miller et al, 1983; Mossman & Gee, 1989).
 - d. Asbestosis patients may also present with superimposed infections because of increased susceptibility caused by immunologic derangements (ATSDR, 1990).
 - e. **CLINICAL PREDICTORS OF OUTCOME** - In a review of 74 cases of asbestos deaths, the 10 year risk of death was increased in the presence of increasing interstitial fibrosis as seen on baseline chest x-ray, dyspnea, low forced vital

capacity, and clinical symptoms of interstitial fibrosis (rales, clubbing and cyanosis) (Markowitz et al, 1997).

B. PLEURAL PLAQUES

1. **DEFINITION** - Pleural plaques are focal, irregular thickenings composed of dense bands of avascular collagen occurring predominantly in the submesothelial parietal pleura (Gefter & Conant, 1988).
2. **SITES** - Plaques may be bilateral and asymmetrical, and are usually located on the parietal pleura of the thorax, diaphragm, mediastinum, or pericardium (Dark & Pingleton, 1983; Mossman & Gee, 1989). Less often, they may occur on the visceral pleura within the interlobar fissure (Gefter & Conant, 1988).
3. **CAUSES** - Although plaques are the most common chest radiographic manifestation of asbestos exposure, no such exposure can be established for 22 percent of autopsy-proven cases (Gefter & Conant, 1988). While the overall incidence of plaques increases with dose, there is no linear correlation between plaque severity and total dust exposure (Gefter & Conant, 1988).
4. **CLINICAL MANIFESTATIONS** - Plaques by themselves are not symptomatic until they become calcified and large enough to restrict chest wall movements and thus affect vital capacity (ATSDR, 1995; Dark & Pingleton, 1983; Dunn, 1989; Gefter & Conant, 1988; Mossman & Gee, 1989).
5. **MALIGNANCY** - Pleural plaques are not lung cancer precursors, although persons with pleural plaques have an increased incidence of lung cancer (ATSDR, 1990; Gefter & Conant, 1988; Mossman & Gee, 1989) and possibly malignant mesothelioma (Bianchi et al, 1997).

C. PLEURAL EFFUSION

1. **INCIDENCE of BENIGN ASBESTOS PLEURAL EFFUSIONS** - The overall incidence of benign asbestos-related pleural effusions was 3.1 percent, with a 7 percent incidence in the heavily exposed group and a 0.2 percent incidence in the indirectly exposed group in one report (Gefter & Conant, 1988). Of all the asbestos-related diseases, it has the shortest latency period, with detection within the first 10 years after exposure (Dunn, 1989; Gefter & Conant, 1988).
2. **CLINICAL MANIFESTATIONS** - Acutely, fever, chest pain, leukocytosis, and an increased erythrocyte sedimentation rate (ESR) may be seen (Dark & Pingleton, 1983; Dunn, 1989).
3. Chronically, there are few, if any, signs or symptoms (Dunn, 1989).
4. The effusions are mostly exudative, sterile, and frequently blood-tinged (Dunn, 1989; Gefter & Conant, 1988; ILO, 1983).
5. Most effusions identified were asymptomatic and small (and often overlooked); as many as 28 percent may recur (Gefter & Conant, 1988).

D. **DIAGNOSIS** - Benign asbestos-related pleural effusion is a diagnosis of exclusion. The differential diagnosis includes mesothelioma, metastatic tumor, tuberculosis, and disease involving the superior vena cava, mediastinal nodes, thoracic duct, or pericardium (Gefter & Conant, 1988).

E. **CLINICAL COURSE** - Although termed "benign, asbestos-related effusions may precede the development of mesothelioma in a small number of patients, necessitating long-term follow-up (Gefter & Conant, 1988). Benign pleural effusions may also lead to functional respiratory impairment because of ensuing fibrosis and pleural thickening (Gefter & Conant, 1988).

o PLEURAL THICKENING

1. **DEFINITION** - Diffuse pleural thickening is a uniform, homogenous, uninterrupted pleural density extending over at least 1/4 of the chest wall with or without accompanying costophrenic angle obliteration (Geffer & Conant, 1988).
2. **CAUSES** - In a series of 1,373 asbestos-exposed workers, 31.4 percent of the cases were related to asbestos exposure, 25.4 percent to confluent plaques, 33 percent to malignant effusion, trauma, infection, or a combination of these, and 10.3 percent were presumed extensions of parenchymal fibrosis (McLoud et al, 1985).
3. **CLINICAL COURSE** - Diffuse pleural thickening may develop as an acute, rapidly progressive process associated with chest pain, or it may assume an indolent, asymptomatic course (Geffer & Conant, 1988). Chronic cases may present with significant pulmonary insufficiency and may require surgical decortication (Geffer & Conant, 1988). Patients presenting with stable pleural plaques are at risk for diffuse pleural thickening and subsequent greater ventilatory impairment (Miller & Miller, 1993).

◦ INTERACTION

1. **SMOKING** - An apparent synergism exists between asbestos-related pulmonary diseases and smoking. The mechanism for this has yet to be established, although several theories have been postulated and tested (Blanc et al, 1988; deShazo et al, 1988; Hobson et al, 1988; Kronenberg, 1989; Mossman & Gee, 1989; Talcott & Antman, 1988; ATSDR, 1995).
 - a. Those who are occupationally exposed to asbestos and who smoke have a 5 to 6 times greater than expected incidence of pleural plaques on chest x-ray in later years (Hillerdal et al, 1983).
 - b. **CASE SERIES** - A retrospective review of shipyard workers found cigarette smoking-asbestos exposure interactions for parenchymal opacities, but not for decreased lung capacity (Blanc et al, 1988). The ILO-interpreted opacities may reflect smoking-associated parenchymal changes among asbestos-exposed smokers.
 - c. Smoking and asbestos exposure were shown to interact and thus decrease mononuclear cell natural killer function (deShazo et al, 1988).
 - d. Smoke-exposed cultures of tracheal implants from rats had a greater number of asbestos fibers in the epithelium and greater proliferative activity, compared to cultures unexposed to cigarette smoke (Hobson et al, 1988).
 - e. Smoking may impair the lung's ability to clear asbestos fibers and thus enhance asbestos-induced fibrogenesis (Mossman & Gee, 1989).
 - f. Lung macrophages, in response to foreign bodies such as asbestos fibers, may release enzymes and oxidants and thus destroy normal lung tissue in the same way that they would react to cigarette smoke (Kronenberg, 1989).

◦ SPUTUM INCREASED

1. **FERRUGINOUS BODIES** - have been found in the sputum of asbestos workers (Stewart & Haddow, 1929).
 - a. McLarty et al (1980) demonstrated a significant association between ferruginous (chalybeate) bodies found in the sputum and radiographic findings of interstitial pulmonary disease, pleural fibrosis, and spirometric abnormalities.
 - b. Increased age and smoking were also related to an increased number of ferruginous bodies (McLarty et al, 1980).
 - c. Although hemolytic activity has been said to be a factor influencing pathogenesis, there

have been few attempts to correlate hemolytic activity with ferruginous bodies (Ayer et al, 1972).

- d. While they are probably formed as a protective mechanism, ferruginous bodies are not biologically inert. Included iron can induce DNA damage and may play a role in formation of hydroxyl radicals and lipid peroxidation (Lund et al, 1994).

- OTHER

1. Asbestos, as a component of industrial dust, may also produce chronic obstructive airways disease, but further study is required to confirm and understand this relationship (Zejda, 1996).

- CARCINOMA

1. RISK FACTOR - Asbestosis patients with progression of small opacities on chest x-ray over several years are at higher risk of developing lung cancer (Oksa et al, 1998). Although smoking history is also a factor in lung cancer, progression of pulmonary fibrosis may be an independent risk factor.

3.10 GENITOURINARY

3.10.1 ACUTE EFFECTS

A. RENAL FAILURE ACUTE

1. CASE REPORT - Acute renal failure has been reported secondary to retroperitoneal fibrosis which developed in a man with diffuse asbestos-related pleural fibrosis (Maguire et al, 1991).

3.13 HEMATOLOGIC

3.13.1 ACUTE EFFECTS

A. LEUKEMIA ACUTE

1. CASE REPORT - Two men who worked in a shipyard for 40 years were diagnosed with acute myelocytic leukemia (Kishimoto et al, 1988).
 - a. The concentrations of asbestos bodies in their lungs were comparable to those in a control group of 10 patients with lung cancer and similar occupational histories.
 - b. Both patients, but none of the controls, had asbestos bodies in the bone marrow.

3.14 DERMATOLOGIC

3.14.1 ACUTE EFFECTS

A. NEOPLASM SKIN

1. ASBESTOS CORNS - Warts or areas of thickened skin surrounding implanted asbestos fibers do NOT lead to skin tumors and disappear on removal of the fibers (ILO, 1983).

3.19 IMMUNOLOGIC

3.19.1 ACUTE EFFECTS

A. IMMUNE SYSTEM DISORDER

1. **COMPLEMENT ACTIVATION** - Asbestos activates complement by an alternative pathway, resulting in leukocyte concentration and lysosomal enzyme release (Dark & Pingleton, 1983).
 - a. With activation of the alternative complement pathway, C5a cleavage product is generated, which serves as a chemotactic agent for alveolar macrophages (Kagan, 1988).
2. **CELLULAR/HUMORAL IMMUNOLOGIC CHANGES** - Reports of serum abnormalities have not been consistent (Nash et al, 1981). Despite some variability, most studies indicate that cell-mediated immunity can be depressed (ATSDR, 1995; Weill & Hughes, 1988). Asbestos, especially chrysotile, can suppress natural killer cell activity and thus interfere with the recognition and destruction of malignant cells (Robinson, 1989).
 - a. Other studies have reported increased cellular immune responses (Anton-Culver et al, 1988; Delclos et al, 1989).
 - b. Elevated bronchoalveolar T4/T8 lymphocyte ratios were noted in 32 subjects with significant asbestos exposure (Delclos et al, 1989).
 - c. Shipyard workers with radiographically detectable asbestosis had greater numbers of T helper and T suppressor cells (disproportionately more of the latter) compared to blood donor controls (Anton-Culver et al, 1988). Increased pokeweed mitogen stimulation was also noted.
 - d. Differences in humoral immune response have also been reported (Anton-Culver et al, 1988; ATSDR, 1995; Talcott & Antman, 1988; Weill & Hughes, 1988).
 - e. Elevated carcinoembryonic antigen levels have been identified with colorectal cancers, but the clinical relevance of elevated immunoglobulins and other serum proteins have yet to be determined (Talcott & Antman, 1988).
 - f. Autoantibodies (rheumatoid factor, antinuclear antibodies) are typically abnormally high in asbestos-exposed workers (ATSDR, 1995; Weill & Hughes, 1988). Caplan's syndrome (pneumoconioses with rheumatoid changes) has been noted in asbestos workers which can lead to rheumatoid arthritis (ATSDR, 1995). In a retrospective study of 109 environmentally-exposed persons, those with pleural plaques had an increased incidence of antinuclear antibodies, as well as increased IgA levels (Zerva et al, 1989).
 - g. Increased levels of anti-double strand DNA antibodies were seen in persons occupationally exposed to asbestos, compared with a non-exposed group (Marczynski et al, 1994).
 - h. Higher IgG and IgA levels were noted among shipyard workers with radiographically detected asbestosis (Anton-Culver et al, 1988). Higher IgG and IgA levels were also noted in environmental (nonoccupational) asbestos exposures. The presence of pleural plaques accentuated the effect on humoral immunity (Zerva et al, 1989).

B. INFECTION

1. **PREDISPOSITION TO INFECTION** - Bronchiectasis and unexplained (but commonly encountered) immunologic deficiencies can predispose an asbestotic patient to infections, including tuberculosis (Baris et al, 1988; Finkel, 1983). Infection can cause further progressive fibrosis, which leads to cor pulmonale.

3.20 REPRODUCTIVE HAZARDS

3.20.1 TERATOGENICITY

A. LACK OF EFFECT

1. MICE - Chrysotile asbestos was not teratogenic in mice (Schardein, 1993).

3.20.2 EFFECTS IN PREGNANCY

A. PLACENTAL BARRIER

1. Uncoated chrysotile asbestos fibers were found in lung, liver, and/or placenta digests of 5 stillborn infants, suggesting transplacental transfer of asbestos (Haque et al, 1992).

3.20.5 MALE REPRODUCTIVE HAZARDS

A. LACK OF EFFECT

1. MICE - No effects on sperm were seen in mice given chrysotile asbestos in the drinking water at 20 mg/kg/day (Rita & Reddy, 1986).

3.21 CARCINOGENICITY

3.21.1 IARC CATEGORY

- #### A. Group 1 - The agent is carcinogenic in humans (evidence in humans: sufficient; evidence in animals: sufficient).

3.21.2 SUMMARY/HUMAN STUDIES

- #### A. Asbestos is a human carcinogen. The primary types of asbestos-related cancers are mesothelioma of the pleura and peritoneum and bronchogenic carcinoma.
- #### B. An association between asbestosis and gastrointestinal, renal, or laryngeal malignancies has been suggested by some reports and refuted by others.

3.21.4 HUMAN STUDIES

A. CARCINOMA

1. TYPES - Primary types of asbestos-related malignancies are bronchial carcinoma and mesothelioma of the pleura and peritoneum (Dunn, 1989; Talcott & Antman, 1988; ATSDR 1995; Crosignani et al 1995). A positive link between asbestos exposure and mesothelioma has been established both epidemiologically and experimentally.
2. Epidemiologic data have conflicting estimates of risk among asbestos workers for developing gastrointestinal cancer and cancers of the larynx, esophagus, pancreas, kidneys, and ovaries (Albin et al, 1990; ATSDR, 1995; Brown et al, 1988; Dark & Pingleton, 1983; Edelman, 1988; Finkelstein, 1989; Frumkin & Berlin, 1988; McLure & Poole, 1990; Molloy et al, 1990; Mossman & Gee, 1989; Neuberger & Kundi, 1990; Parnes, 1990; Raffn et al, 1989; Sebastien et al, 1989; Sluis-Cremer & Bezuidenhout, 1988; Smith, 1990; Smith et al, 1989, 1990; Talcott et al, 1989; Weiss, 1990; Demers et al, 1994; Kraus et al, 1995).

B. PREDISPOSING FACTORS

1. CONFOUNDING/SYNERGISTIC FACTORS - The cancer-causing ability of asbestos

seems to be related to fiber length, type, size, geometry, and insolubility in aqueous solutions (Brown et al, 1990; Churg et al, 1989; Gibbs, 1990; ILO, 1983; Lippman, 1988; McDonald et al, 1989; Mossman & Gee, 1989; Sebastien et al, 1989; Spurny et al, 1983; ACGIH, 1991).

- a. Asbestos fibers in order of toxicity are - crocidolite, amosite, and chrysotile.
 1. In a fatality due to widely metastatic malignant mesothelioma, asbestos fibers were extracted from many tissues, including lungs, pleura, pericardium, tunica vaginalis testis, lymph nodes with tumor metastasis, small intestine, liver, spleen and kidney. All tissues examined contained asbestos fibers, with lung parenchyma containing numerous fibers (Watanabe et al, 1994). The precise mechanism of carcinogenesis by asbestos fibers is unclear. The role of pulmonary macrophages has been postulated.
 - b. Respirable particles are generally between 0.5 and 5 microns in diameter, with a length-to-width ratio of 3:1. However, in the case of asbestos, some fibers as large as 10 microns in diameter may penetrate to the lower pulmonary regions (ATSDR, 1990).
 1. An increased incidence of lung cancer has been produced by fibers longer than 5 microns (ATSDR, 1995).
 2. TRACE METALS - Some authors think that trace metals may contribute to asbestos' cancer-causing abilities. Nickel, cobalt, chromium, manganese, and iron have been found in samples of amosite, crocidolite, and chrysotile (Roy-Chowdhury et al, 1973).
 3. SMOKING - Generally, lung cancer occurs with heavy asbestos exposure; the incidence is increased among smokers (Geffer & Conant, 1988; Mossman & Gee, 1989; Newhouse, 1983; Robinson, 1989). However, the synergistic effect of smoking and asbestos on development of cancers of the stomach, colon-rectum, and kidney has not yet been confirmed (ATSDR, 1990). In addition, the effects of asbestos exposure on the risk of developing mesothelioma does not appear to be increased by smoking (Clayton & Clayton, 1993; ATSDR, 1995).
 - a. Smoking may impair the lung's ability to clear asbestos fibers, and may enhance asbestos-induced fibrogenesis (Mossman & Gee, 1989).
 - b. Rat studies showed that asbestos potentiates physical transport of adherent molecules (including hydrocarbon carcinogens) into the lung where phagocytosis of asbestos fibers incorporates hydrocarbons into pulmonary macrophages (Talcott & Antman, 1988).
 4. ASBESTOSIS - While individuals with radiographic or clinical evidence of asbestosis probably have, on average, a higher risk of cancer due to heavier exposure to asbestos (Edelman, 1990); asbestosis is not required for increased cancer risk in those with asbestos exposure. Cancer risk is increased even in the absence of overt asbestosis (Finkelstein, 1997; Hillerdal & Henderson, 1997; Egilman & Reinert, 1996).
- C. RISK FACTORS
1. EVIDENCE OF CAUSATION includes the following -
 - a. DOSE-RESPONSE - The chance of developing tumors is dose-related to asbestos exposure, but there is no "critical level" where the risk of cancer is zero (ATSDR, 1990). No known threshold for asbestos induced lung cancer has been established (ATSDR, 1995).
 - b. Although mesothelial tumors may have a long latency period of up to 68 years, these may occur with exposure of less than one year duration (ATSDR, 1990; Mowe et al, 1984; Newhouse, 1983).
 1. A multiplicative relative risk of 1.9 for mesothelioma was estimated for each

- fiber-year/mL of exposure (Albin et al, 1990).
2. The rate of mesothelioma continues to rise, with estimated lifetime risks of 1.3 percent in British persons born between 1893 and 1948, 1.0 percent in those born between 1943 and 1948, and 0.6 percent for those born between 1948 and 1953.
3. According to one model, deaths from mesothelioma will peak in approximately the year 2020, and may account for 1 percent of all deaths for men born in the 1940's (Peto et al, 1995).
2. **CONSISTENCY/RISK ESTIMATES** includes the following -
 - a. Risk estimates for bronchogenic cancer among workers with asbestosis or significant exposure to asbestos have not been consistently high. This variability can be due to methodological differences.
 - b. Although persons exposed to asbestos by inhalation have a twofold greater risk of colorectal cancer than unexposed individuals, data were conflicting and insufficient to clearly relate GI tumors or peritoneal mesotheliomas to direct ingestion of asbestos fibers (Albin et al, 1990; ATSDR, 1990; Edelman, 1988; Weiss, 1990).
 - c. A 3.4-fold increase in mortality from malignancy (compared to expected rates) has been noted among workers in a factory where the average asbestos level was 80 particles/mL and where crocidolite-containing cigarette filters were manufactured (Talcott et al, 1989).
 - d. In one study of mesothelioma cases among miners and millers, amphibole (crocidolite and amosite), chrysotile, and tremolite were found in lung fibers and were highest among workers with mesothelioma (Dufresne et al, 1995).
3. **TEMPORALITY** is shown as follows -
 - a. Reports of asbestosis and colorectal cancer showed only temporality of association and not causality (Weiss, 1990).
4. **BIOLOGIC SENSE** is shown as follows -
 - a. Asbestos fibers have been identified within some human specimens of colorectal adenocarcinomas and in extrapulmonary tissues, including tonsils, thoracic and abdominal lymph nodes, small intestines, pancreas, kidneys, and bone marrow (ATSDR, 1990; Finkel, 1983; Smith et al, 1989). This establishes only site-specific evidence of exposure, not causation (Weiss, 1990).
 - b. Lung cancer patients had significantly higher levels of ferruginous bodies in lung digests than did controls, even though only one cancer patient had any known exposure to asbestos (Warnock & Churg, 1975). This finding suggests that asbestos may be commonly involved in lung cancer.
 - c. Animal studies revealed that asbestos fibers can penetrate the GI tract (ATSDR, 1990). Tumorigenesis has also been noted in animal bioassays (Smith et al, 1989).
5. **OZONE** effects are shown as follows -
 - a. Prolonged exposure to low levels of ozone appears to impair clearance of asbestos from the lungs. In a study of rats exposed to low levels of ozone for 6 weeks and then exposed to aerosolized asbestos fibers for 5 hours, fiber mass and fiber number were significantly greater ($P<0.05$) than that of a control group of rats exposed only to aerosolized asbestos (Pinkerton et al, 1989).

D. MESOTHELIOMA

1. Mesothelioma is a rapidly invasive and fatal malignancy associated with asbestos exposure (ATSDR, 1990; Neuberger & Kundi, 1990; Newhouse, 1983; Roggli et al, 1993).
 - a. Andersson & Toren (1995) suggested that in Sweden there may be an under

reporting of mesothelioma as an occupational disease.

2. CLINICAL PRESENTATIONS include the following -
 - a. A large unilateral pleural effusion is the most frequent presenting manifestation of malignant mesothelioma (Gefter & Conant, 1988). Uncommonly, mesothelioma may present as a solitary pleural mass.
 - b. A characteristic aching, nonpleuritic chest pain may precede development of any radiographic findings (Gefter & Conant, 1988; Miller, 1990).
 - c. A small percentage of patients may present with repeated episodes of benign pleurisy with resolving effusions (Gefter & Conant, 1988).
 - d. Abdominal pain, a palpable mass, or increased abdominal girth are the usual presenting symptoms of peritoneal mesothelioma (Talcott & Antman, 1988).
 - e. Pericardial effusion and tamponade, brachial plexopathy, Horner's syndrome, dysphagia, and the superior vena cava syndrome are less common presentations (Talcott & Antman, 1988).
3. CLINICAL COURSE - The 1-year survival rate of mesothelioma patients is less than 30 percent; no efficacious treatment has been identified, although intensive multimodality therapy has been shown to prolong the disease-free interval (ATSDR, 1990; Newhouse, 1983; Talcott & Antman, 1988).
4. DOSE-RESPONSE RELATIONSHIP - Although there is a correlation between asbestosis and risk of mesothelioma, pleural and peritoneal tumors may occur with exposures of less than a year (ATSDR, 1990; Newhouse, 1983). A multiplicative relative risk of 1.9 was estimated for each fiber-year/mL of exposure (Albin et al, 1990).
5. SMOKING - Unlike asbestos-related bronchogenic carcinoma, mesothelioma risk does not appear to be influenced by smoking (ATSDR, 1995; Berry et al, 1985; Muscat & Wynder, 1991).
6. FAMILIAL MESOTHELIOMA - Reports of mesothelioma among family members with no direct occupational exposure to asbestos have been reported and attributed to "bystander" exposure to other family members who have direct asbestos exposure (Huncharek et al, 1989; Li et al, 1989; Giarelli et al, 1997; Schneider et al, 1996; Maltoni et al, 1995; Dodoli et al, 1992; ATSDR, 1995). Others have suggested the role of genetic factors (Hammar et al, 1989).
 - a. Two genotypes have been identified with increased risk of mesothelioma: GSTM null, and NAT2 (slow-acetylator). Each confers a 2-fold increased risk, and individuals with both genotypes have a 4-fold higher risk; when combined with asbestos exposure, this risk increases to 7-fold, compared to those with "beneficial" genotypes GSTM1 and NAT2 (fast-acetylator) (Hirvonen et al, 1995).
7. COMMUNITY ACQUIRED EXPOSURE - Numerous reports and case series have been published which document an increased risk of mesothelioma in non-asbestos workers in various locations where local asbestos industries exists (Berry, 1987; Magnani et al, 1997; Rogers & Nevill, 1995). Local asbestos bearing deposits also appear to increase risk (Selcuk et al, 1992). In some cases, local asbestos containing minerals are used to produce whitewash (Sakellariou et al, 1996; Constantopoulos et al, 1991).
8. FIBER TYPE effects include the following -
 - a. In a retrospective study of 94 asbestos related mesotheliomas, Roggli et al (1993) found amosite asbestos in 81 percent of the cases which accounted for 58 percent of all fibers 5 mcm of greater in length. Tremolite/actinolite/anthophyllite were found in 55 percent of all cases; chrysotile was found in 21 percent of all cases; crocidolite was found in 16 percent of all cases. This suggests that crocidolite asbestos may not be responsible for most mesotheliomas in the USA.

E. PULMONARY CARCINOMA

1. BRONCHOGENIC CARCINOMA is a major cause of death in asbestos-exposed workers (estimated to affect 20 to 25 percent of heavily exposed workers) because of the combined risks of smoking and asbestos (Geffer & Conant, 1988).
2. The latency period ranges from 15 to 35 years following exposure (Geffer & Conant, 1988). The prevalence is greater in those persons handling finished products than in miners or millers (Dark & Pingleton, 1983).
3. Adenocarcinomas are most frequently seen (ATSDR, 1990; Dark & Pingleton, 1983; Geffer & Conant, 1988; Mollo et al, 1990; Talcott et al, 1989). Other tumors were characterized as adenomas and squamous cell carcinomas (ATSDR, 1995).
4. There are no diagnostic clinical or radiographic features to indicate that a given lung cancer has been caused by asbestos (Geffer & Conant, 1988). However, most asbestos-related tumors are peripheral lower lobe lesions (Geffer & Conant, 1988; Karjalainen et al, 1993).
5. Risk estimates for bronchogenic cancer among workers with asbestosis or significant exposure to asbestos have not been consistently high. This variability can be due to methodological differences, or to individual differences in susceptibility.
 - a. A case-control study of 175 lung cancer patients and 176 controls showed a strong and significant association between asbestos exposure and small cell carcinoma (Relative Risk = 3) and a weaker, but equally significant, association with adenocarcinoma (RR = 2.2) (Kjuus et al, 1986).
 - b. Although an increased mortality and morbidity from respiratory cancer was noted in a cohort of asbestos cement workers compared to unexposed industrial workers, the overall risk for respiratory cancer (excluding mesothelioma) was not increased compared to the general population (Albin et al, 1990).
 - c. Deaths from lung cancer in asbestos cement workers were not significantly different after adjustments for age and smoking (Standardized Mortality Ratio (SMR) decreased from 1.7 to 1.04) (Neuberger & Kundi, 1990).
 - d. Necropsy studies of 339 amphibole asbestos miners stressed the significant association between asbestosis (and not merely asbestos exposure) and bronchial cancer (Sluis-Cremer & Bezuidenhout, 1989).
 - e. The risk for lung cancer was higher in persons with radiologic evidence of pulmonary fibrosis, but the risk was also elevated in persons with asbestos exposure and no fibrosis (Wilkinson et al, 1995).
 - f. A case control study failed to confirm asbestos exposure, but concluded that there was no association between lung cancer and the duration of employment in automotive parts factories (Finkelstein, 1989).
 - g. Excess risk for cancer of the lung (Relative Risk 1.8; 95 percent Confidence Interval = 1.54 to 2.1), pleura (RR = 5.46, 95 percent; CI = 2.62 to 10.05), and mediastinum (RR = 5; 95 percent CI = 1.01 to 14.61) were found in a cohort study of 7,996 men and 584 women employed in the Danish asbestos cement industry where fiber levels were more than 0.5 to 2 fiber/mL (Raffn et al, 1989).

F. LARYNX CARCINOMA

1. Risk estimates for laryngeal cancer among workers with asbestosis or significant exposure to asbestos have not been consistently high. This variability could be due to methodological differences, or to differences in individual susceptibility.
 - a. A matched case-control interview study that corrected for potential confounding by cigarette smoking and alcohol consumption showed a nonsignificant but elevated risk (Relative Risk = 1.46; 95 percent Confidence Interval = 0.98 to 2.18) for laryngeal carcinoma among those with occupational asbestos exposure (i.e., among boilermakers, sheetmetal workers, pipefitters/plumbers, and carpenters)

(Brown et al, 1988).

- b. A case control study failed to confirm asbestos exposure, but concluded that there was no association between laryngeal cancer and the duration of employment in automotive parts factories (Finkelstein, 1989).
 - c. The cross-sectional and longitudinal data derived from personnel in a brake manufacturing plant did not support asbestos as an etiologic factor for laryngeal cancer, but an irritant effect of asbestos was suggested (Parnes, 1990).
 - d. An excess risk of laryngeal cancer (RR = 5.5; 95 percent CI = 1.77 to 12.82) was found among a group of workers first employed in the Danish asbestos cement industry where fiber levels were more than 0.5 to 2 fiber/mL from 1928 to 1940 (Raffn et al, 1989).
 - e. After correcting for smoking and alcohol consumption, workers heavily exposed to asbestos (with lung cancer relative risk estimates of 4.06 and 3.28) also had high relative risk estimates for laryngeal cancer (RR = 1.91; 90 percent CI = 1 to 3.34 and RR = 3.75; 90 percent CI = 1.01 to 9.68, respectively) (Smith et al, 1990).
2. No clear dose-response relationship with laryngeal cancer was noted when asbestos exposure in the Texas Gulf Coast was analyzed by duration of exposure, but a positive gradient was found when asbestos was categorized by intensity of exposure (Brown et al, 1988).

G. GASTRIC CARCINOMA

1. Risk estimates for gastrointestinal cancer among workers with asbestosis or significant exposure to asbestos have not been consistently high, and have been noticeably much lower than those reported for lung cancer and mesothelioma (Talcott & Antman, 1988). This variability can be due to methodological differences or to different individual susceptibilities.
 - a. A review of published studies on independent cohorts of asbestos workers showed no consistently higher standardized mortality ratios (SMRs) among exposed compared to unexposed populations and no apparent dose-response relationship was observed (Edelman, 1988).
 - b. A meta-analysis and review of published cohort data stratified cohorts by dose and showed that significant asbestos exposure (as indicated by a lung cancer standardized mortality ratio (SMR) of at least 200) is associated with an elevated gastrointestinal cancer SMR (Frumkin & Berlin, 1988).
 - c. A case control study did not confirm asbestos exposure, but concluded that there was no association between gastrointestinal cancer and duration of employment in automotive parts factories (Finkelstein, 1989).
 - d. Excess risk for gastric cancer (Relative Risk = 1.43; 95 percent Confidence Interval = 1.03 to 1.93) was found in a cohort study of 7,996 men and 584 women employed in the Danish asbestos cement industry, where fiber levels were more than 0.5 to 2 fibers/mL (Raffn et al, 1989).
 - e. No overall excess risk from cancer of the upper and lower gastrointestinal tract was found in a cohort of asbestos cement workers compared to a local reference cohort of unexposed industrial workers (Albin et al, 1990). Another case-control study also failed to find an association between colon cancer and asbestos exposure (Garabrant et al, 1992).
 - f. Norwegian lighthouse keepers, who consumed cistern drinking water contaminated with asbestos from runoff from asbestos-cement roof tiles for two decades, had an excess risk of stomach cancer, but not malignant mesothelioma (Andersen et al, 1993).
 - g. Colorectal cancer occurred with an estimated increase of 1.6 percent in the

incidence density ratio for each fiber-year/mL of asbestos exposure, but no relationship was found between development of colorectal cancer and duration of exposure (Albin et al, 1990). A two-fold increase in colon cancer was related to high-level asbestos exposure in one case-control study (Fredriksson et al, 1989).

- h. A review of published data from 21 cohorts of asbestos-exposed workers found a 0.97 estimate of the summary standardized mortality or morbidity ratio for colorectal cancer and no dose-response relationship between asbestos exposure and colorectal cancer (Weiss, 1990).
2. Reports suggest that ingested asbestos is excreted in the feces and that malignancy could be caused by swallowed asbestos fibers removed from the lung upper respiratory regions by the ciliary mechanism (ATSDR, 1990).

H. RENAL CARCINOMA

1. GENITAL CANCER - Excess risk for cancer of male genital organs (Relative Risk = 3.03; 95 percent Confidence Interval = 1.11 to 6.6) was as found in a cohort study of 7,996 men and 584 women employed in the Danish asbestos cement industry where fiber exposure levels were more than 0.5 to 2 fibers/mL (Raffn et al, 1989).
2. RENAL CANCER - Excess mortality from kidney cancer among asbestos-exposed workers was noted in a review of occupational cohort studies of insulators (Standardized Mortality Ratio = 2.22; 90 percent CI = 1.44 to 3.3), asbestos products company workers (SMR = 2.76; 90 percent CI = 1.29 to 5.18), and shipyard workers (SMR 1.98; 90 percent CI = 1.42 to 2.7) (Smith et al, 1989).
3. Case control studies with low prevalence of heavy asbestos occupational exposure are unable to provide evidence for or against a possible association between asbestos exposure and kidney cancer (Smith, 1990).
4. An association between asbestos exposure and renal cell cancer was seen in an international case-control study of 1732 cases (Mandel et al, 1995).
5. An association between asbestos exposure and bladder cancer was reported in one case-control study (Bravo et al, 1988).

I. OVARIAN CARCINOMA

1. Heller et al (1999) reported that there appears to be evidence that exposure to asbestos increases the risk of developing ovarian cancer.

J. LYMPHOMA-LIKE DISORDER

1. Increased risk for non-Hodgkin's lymphoma has been associated with asbestos exposure (Ross et al, 1982), but this finding was not replicated in a subsequent report (Olsson & Brandt, 1983).

K. LEUKEMIA LYMPHOCYTIC

1. B-CELL CANCERS - A modest dose-related increase in chronic lymphocytic leukemia, but not multiple myeloma, was seen in one case-control study (Schwartz et al, 1988). Another study confirmed a lack of association between asbestos exposure and multiple myeloma (Boffetta et al, 1989).

3.21.5 ANIMAL STUDIES

A. PULMONARY CARCINOMA

1. Pulverized asbestos pipe covering dust induced pulmonary carcinomas in rats exposed to 85 mg/m(3) for 6 hours/day, 5 days per week for 7 months, followed by a lifetime period of observation (Leong et al, 1978).

B. MESOTHELIOMA

1. A single injection of each of the following kinds of fibers was sufficient to induce

mesotheliomas in hamsters: soft chrysotile, harsh chrysotile, amosite, diatomaceous earth, crocidolite, and anthophyllite (Smith, 1984).

C. LACK OF EFFECT

1. Chrysotile asbestos was not carcinogenic by the oral exposure route in hamsters when given at a level of 1 percent in the diet over the animals' lifetime (NTP, 1990).

3.22 GENOTOXICITY

3.22.2 DNA DAMAGE/REPAIR

- A. Asbestos can induce DNA damage; its activity is enhanced several-fold by peroxides (Mahmood et al, 1993; Mahmood et al, 1994). Asbestos can form complexes with iron cations; iron-complexed asbestos reacts with peroxides to generate free radicals. The extent of DNA damage is proportional to the amount of active iron complexed with asbestos (Ghio et al, 1994; Lund et al, 1994).
 1. Iron contained in ferruginous bodies can also induce DNA damage if it is in the ferrous form (Lund et al, 1994).
- B. A 2- to 4-fold elevation in double-stranded DNA breaks was seen in lymphocytes of persons occupationally exposed to asbestos, compared with non-exposed controls (Marczynski et al, 1994).

3.22.3 MUTAGENICITY

- A. In general, asbestos has not been mutagenic in bacteria and is not clearly genotoxic in mammalian cells, except for some rodent cells in vitro (Daniel, 1983; Chamberlain & Tarmy, 1977; Daniel, 1983). Amosite, crocidolite, and chrysotile were not mutagenic in the HGPRTase assay in rat cells (Reiss et al, 1982).
- B. Developments in molecular genetics have enabled mutations induced by asbestos to be detected in mammalian cells.
 1. Asbestos can induce multilocus deletions in human-hamster hybrid cells; these mutations are prevented by catalase, superoxide dismutase, or anti-oxidant enzymes (Hei et al, 1995).
 2. Crocidolite, but not chrysotile, induced loss of heterozygosity in the HLA-A locus in human peripheral lymphocytes (Both et al, 1994).
- C. Induction of mutations in specific genes (oncogenes) is thought to be part of the mechanism of carcinogenesis for some cancers.
 1. Lung tumor specimens from lung cancer patients showed a high frequency of a specific kind of ras oncogene mutation: 57 percent of the adenocarcinoma samples had K-ras mutations. K-ras mutations were elevated 4.9-fold in samples from heavy smokers and 2.2-fold with occupational exposure to asbestos. While the latter elevation was not statistically significant, it suggests that asbestos may play a role in inducing K-ras mutations (Husgafvelpursiainen et al, 1993).

3.22.4 CHROMOSOME ABERRATIONS

- A. Sister chromatid exchange (SCE) frequency was increased in a sample of 22 asbestos cement workers compared to matched controls (Fatma et al, 1991).
- B. CYTOGENETIC ANALYSIS OF ASBESTOS-RELATED TUMORS - Seven mesothelial cell lines were established from clinical specimens from 5 patients with asbestos-related pleural

mesothelioma (Pelin-Enlund et al, 1990). Karyotype analysis revealed complex structural and numerical abnormalities.

- C. Normal human mesothelial cells exposed for 48 hours to crocidolite, amosite, and chrysotile had a significant increase in cells with numerical and structural chromosomal abnormalities (Olofsson & Mark, 1989). Human amnion cells and syrian hamster embryonic fibroblast cells demonstrated similar phenomena (Dopp et al, 1997).
- D. Crocidolite enhanced aneuploidy but induced few structural aberrations in cultured mouse mesothelial cells (Yegles et al, 1993).
- E. Elevations in SCEs and chromosome aberrations were seen in cultured lymphocytes of asbestos cement workers (Fatma et al, 1991). SCE's are also reported to be elevated in an area of Turkey with endemic asbestiform mineral deposits (Donmez et al, 1996).
- F. Previous in vivo exposure to asbestos has been associated with increases in stable chromosome aberrations in human lymphocytes, visualized by fluorescent in situ hybridization with whole chromosome probes ("chromosome painting") (Ramsey et al, 1995).
- G. Amosite, crocidolite, and chrysotile all induced micronuclei in cultured hamster embryo cells (Dopp et al, 1995).
- H. Chrysotile and zeolite particles given intraperitoneally can induce chromosome aberrations in mice (Durnev et al, 1993). Chrysotile induced chromosome aberrations in Chinese hamster cells (Aravinda Babu et al, 1980; Sincock & Seabright, 1975; Oshimura et al, 1984). Chinese chrysotile induced SCEs in human cells (Hong & He, 1985).
- I. MITOTIC DELAY - was induced in human fibroblasts with asbestos dust exposure; this did not cause a dose-related increase in the frequency of sister-chromatid exchanges (Casey, 1983).

3.22.5 OTHER

A. GENE ACTIVATION is expressed as follows -

- 1. Asbestos can induce expression of c-fos and c-jun oncogenes in rat pleural mesothelial cells; crocidolite was more active than chrysotile for this effect, as it is for induction of mesothelioma (Heintz et al, 1993).
- 2. It also induces c-jun mRNA in hamster tracheal epithelial cells, progenitors for bronchogenic carcinoma; this induction can respond to either asbestos or hydrogen peroxide, and confers the ability of cells to grow in soft agar (an endpoint of in vitro malignant transformation) (Timblin et al, 1995).
- 3. Crocidolite asbestos induced proteins in hamster tracheal epithelial cells which bound to nuclear factor kappa-B, a transcription factor which regulates genes in inflammatory and proliferative processes. Induction of mRNA for some of these NF-kappa-B-dependent genes, including c-myc, was shown by Northern blot analyses (Janssen et al, 1995).

3.23 OTHER

3.23.1 ACUTE EFFECTS

A. FATIGUE

- 1. Fatigue and weight loss are common in patients with asbestosis (ATSDR, 1990).

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ASBESTOS

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4.0 MEDICAL SURVEILLANCE/LABORATORY

4.1 MONITORING PARAMETERS/LEVELS

4.1.1 SUMMARY

- A. Chest X-ray and pulmonary function tests should be monitored in asbestos-exposed patients.

4.1.2 SERUM/BLOOD

A. BLOOD/SERUM CHEMISTRY

1. SERUM PEPTIDE LEVELS - Serum type III procollagen peptide (PIIP; a lung structural protein precursor) concentrations were shown to be significantly higher among 36 asbestos-exposed workers, compared to 13 healthy controls; the levels were significantly related to duration of asbestos exposure (Cavalleri et al, 1988). This potential diagnostic tool has yet to be validated.

4.1.5 OTHER

A. MONITORING

1. PULMONARY FUNCTION TESTS - After correcting for smoking, age, and other confounders, a restrictive pattern of pulmonary dysfunction with preserved diffusing capacity is expected in patients with asbestosis, unless severity impairs diffusion as well (ATSDR, 1990; Demers et al, 1990; Jones et al, 1988; Kilburn & Warshaw, 1990, 1990a; Mossman & Gee, 1989; Robins & Green, 1988; Schwartz et al, 1990, 1990a; Siracusa et al, 1988).
 - a. Nonsmoking patients with asbestosis typically have spirometric changes indicative of small airway disease and restrictive defects; smokers with asbestosis may have a combined obstructive/restrictive pattern (ATSDR, 1990; Mossman & Gee, 1989).
 - b. Smoking-adjusted forced vital capacity (FVC) and forced expiratory volume at one second (FEV1) decreased with increasing years of work as boilermakers (Demers et al, 1990). These respiratory function changes were also noted among other asbestos exposed workers (Robins & Green, 1988; Siracusa et al, 1988). Cessation of asbestos exposure for about 10 years did not arrest lung function decline (Siracusa et al, 1988).
 - c. Linear multivariate regression analysis which controlled for potential confounders showed that asbestos-induced circumscribed plaques and diffuse pleural thickening were independently associated with decrements in FVC, but not with decrements in the FEV1/FVC ratio (Schwartz et al, 1990).
 - d. Of 24 nonsmoking sheet metal workers, all had normal parenchyma on chest x-ray

postero-anterior view, 7 had normal pleura, 9 had circumscribed plaques, and 8 had diffuse pleural thickening (Schwartz et al, 1990a). Those with pleural thickening had lower FVC, total lung capacity, and CO-diffusing capacity. Those with plaques had reduced FVC.

- e. Significant pulmonary dysfunction (reduced FEV1, FVC, terminal flow, and increased thoracic gas volume) were associated with pleural asbestos signs (plaques or diffuse pleural thickening) among men who never smoked (Kilburn & Warshaw, 1990, 1990a). Current and ex-smokers had additional dysfunction, even after adjustment for duration of smoking.
- f. Patients with combined obstructive/restrictive patterns should be followed with studies of carbon monoxide diffusion capacity and static lung volumes (ATSDR, 1990).

B. OTHER

1. **LUNG BIOPSY** - Open lung biopsy is the only definitive diagnostic test for asbestosis (ATSDR, 1990).
 - a. Pathologic diagnosis requires the presence of diffuse interstitial fibrosis and asbestos bodies in tissue sections (Churg, 1989).
 - b. Asbestos bodies identified on a histologic section of a hilar lymph node are generally indicative of a heavy asbestosis lung burden (Roggli & Benning, 1990).
 - c. Asbestos fiber counts in lung may also be useful in confirming a diagnosis of asbestosis and appear in some studies to correlate with severity of pulmonary fibrosis (Green et al, 1997) and with other indices of exposure (Karjalainen et al, 1996).
 - d. The asbestos lung burden has also been used for confirming asbestos-related mesothelioma (Kishimoto et al, 1989a; Warnock, 1989).
2. **SPUTUM STUDIES** - Sputum inspection for asbestos fibers or ferruginous bodies lacks sensitivity and specificity (ATSDR, 1990; McDonald et al, 1992). However, sputum cytology remains a useful diagnostic test for neoplasia and lung cancer (ATSDR, 1990). Election microscopy analysis of sputum may be effectively used to assess exposure to asbestos (Harber & Smitherman, 1991).
3. **BRONCHOALVEOLAR LAVAGE** - Bronchoalveolar lavage (BAL) has been recommended as an adjunct in the diagnosis of asbestos-related pulmonary diseases (Barbers & Abraham, 1989; Delclos et al, 1989; Hayes et al, 1989).
 - a. Amosite fibers were noted in a sample obtained by bronchoalveolar lavage and analyzed with scanning electron microscopy-energy dispersive x-ray (Barbers & Abraham, 1989), confirming the diagnosis in a 55-year-old man who had typical clinical and radiologic evidence of asbestosis 36 years after exposure for less than a year, but a negative transbronchial lung biopsy.
 - b. Bronchoalveolar lavage detected significant increases in neutrophils and T4/T8 ratios among 32 asbestos-exposed males compared to controls (Delclos et al, 1989). Because the simultaneously increased gallium scan activity did not correlate with radiological and functional parameters, BAL and gallium scan may reflect inflammation that is not clinically apparent.
 - c. Bronchoalveolar lavage and gallium scans were abnormal in varying proportions of asbestos-exposed workers with definitive, equivocal, and no chest x-ray evidence of pneumoconioses, suggesting a possible role in detecting active subclinical inflammation (Hayes et al, 1989).
4. **OTOLARYNGOLOGIC EXAMINATION** - Asbestos workers with hoarseness, pain, or soreness of the throat should be referred for a detailed otolaryngologic examination of the upper respiratory tract looking for the presence of laryngeal cancer (HSDB, 1995).

5. OSHA REQUIREMENTS - OSHA has specific clinical monitoring requirements for workers exposed to asbestos. Refer to the Micromedex, Inc REGSLINK(R) Information System for more information.

4.2 RADIOGRAPHIC STUDIES

A. CHEST RADIOGRAPH

1. The sensitivity and specificity of radiographic studies for detection of plaques and asbestos-exposure are varied, because of different radiographic and patient selection criteria. False positive readings (compared to autopsy findings) ranged from 8.4 to 58 percent, and false negatives ranged from 60 to 92 percent (Geffer & Conant, 1988).
 - a. In autopsy series, pleural plaques have been identified in approximately one-third to one-half of persons 20 years after significant asbestos exposure, and many of these plaques were not identified on antemortem x-rays (Talcott & Antman, 1988).
2. Radiographically-detected pleural plaques have been shown to correlate well with asbestos bodies on autopsy if the lung burden is more than 500 asbestos bodies/5 grams of autopsy lung tissue (Kishimoto et al, 1989).
3. The association of pleural thickening and calcification enhances diagnostic accuracy (ATSDR, 1990). There are several conditions which can mimic asbestos-related diseases, including scarring adjacent to old disease, trauma, fat or muscle shadows, healed tuberculosis, histoplasmosis, and other conditions (Reger et al, 1990).
4. Using the ILO criteria, as many as 10 to 20 percent of workers with histological evidence of asbestosis will have normal chest x-ray films (Rockoff & Schwartz, 1988). In the other extreme, positive radiographical ILO readings of pulmonary fibrosis have been found with normal lungs.
5. Variations in classifying pleural changes and inadequacy in describing features believed to be important by some readers were problems identified with the ILO 1980 International Classification of the Radiographic Appearances of Pneumoconioses (Rossiter et al, 1988). A survey found an intraobserver variation of 3.9 percent, and an interobserver variation of 18 percent (Geffer & Conant, 1988).
6. Despite the discrepancies between histologic and radiographic diagnosis, roentgenographic interpretations are still deemed useful however subjective they may be (Ducatman, 1989).
7. Because of intra- and interobserver variations in interpretations, chest x-rays are only supportive diagnostic tools (Geffer & Conant, 1988). An ILO grade of less than 1/0 implies that the diagnosis is unlikely, but diagnosis still rests on multiple clinical criteria (Geffer & Conant, 1988; Schwartz et al, 1988).
8. Reviews of smoking and roentgenographic opacities in asbestos workers suggest that parenchymal opacities alone will not reliably differentiate between the impacts of asbestos exposure and smoking in patients who have both risk factors (Blanc et al, 1988; Ducatman et al, 1990; Hnizdo & Sluis-Cremer, 1988). A cross-sectional study confirmed that smoking can be dose-related with parenchymal, but not pleural, changes (Delclos et al, 1990).
9. CT scan has been recommended as a sensitive means of differentiating asbestos-related pleural plaques from soft-tissue densities (ATSDR, 1990).
10. The strong association of both circumscribed plaques and diffuse pleural thickening with parenchymal fibrosis on high-resolution computerized tomography (HRCT) suggest that HRCT scan may be useful in identifying parenchymal injury not detected with postero-anterior chest radiographs (Schwartz et al, 1990a; Neri et al, 1996).

- a. HRCT detected pleural and/or pulmonary involvement in a group of 72 asbestos-exposed workers who did not have clear evidence of lung disease on chest radiographs (Falaschi et al, 1995).
11. Gallium scanning and/or bronchoalveolar lavage have been recommended as adjuncts for the detection of active (even subclinical) pulmonary inflammation in asbestos-exposed workers (Barbers & Abraham, 1989; Delclos et al, 1989; Hayes et al, 1989).
12. A prospective study of 3893 shipyard workers found no strong association between different exposure parameters (eg, chest radiographs, spirometry, and questions about smoking habits, asbestos exposure, and respiratory symptoms) and risk of mesothelioma. Traditional health monitoring parameters appear to be of little value in assessing persons with a high risk of mesothelioma following asbestos exposure (Sanden & Jaruholm, 1991).

B. RADIOGRAPHIC-OTHER

1. Chest x-ray is useful, but the diagnosis is often difficult to make from x-rays taken early in the disease process, especially as there do not appear to be any pathognomonic radiographic findings in asbestosis (Geffer & Conant, 1988).
2. Oblique postero-anterior chest x-ray views are sometimes useful (Geffer & Conant, 1988; Newhouse, 1983).
3. Localized fibrous thickenings 3 to 5 mm in size in the parietal pleura are the most common asbestos-related changes on chest radiographs (Talcott & Antman, 1988).
4. Only minor pleural changes are seen 10 to 20 years after initial exposure; calcification is apparent on chest radiographs after 20 years (Talcott & Antman, 1988).
5. In early cases, blunting of the costophrenic zones may be seen (Geffer & Conant, 1988; Lilis et al, 1988). Diffuse pleural thickening with concomitant blunted costophrenic angle is also the most frequent residual radiological abnormality after benign pleural effusion (Lilis et al, 1988).
6. The "shaggy" cardiac border described in advanced asbestosis is an uncommon finding (Talcott & Antman, 1988).
7. Pleural effusion occurs in 3 to 5 percent of asbestos workers as early as 3 years after the first exposure. Rule out primary or secondary pleural malignancies and other entities such as tuberculosis. A unilateral pleural effusion more than 20 years after asbestos exposure suggests malignant mesothelioma (Talcott & Antman, 1988).
8. In a general health survey, men 30 to 59 years old had a 2.7 percent incidence of pleural effusions in non-asbestos exposed individuals and a 5.7 percent incidence in asbestos exposed individuals. The authors estimated that 10 percent or more of cases of pleurisy (with effusion) could be associated with asbestos exposure (Malberg & Hillerdal, 1990).
9. Thickened lobar fissures, especially with extensive pleural abnormalities, suggest mesothelioma (Talcott & Antman, 1988).
10. A positive gallium scan indicates lung inflammation and predicts a decline in FVC and the development of progressive radiographic abnormality (Harber & Smitherman, 1991).

4.3 METHODS

A. OTHER

1. OSHA REQUIRED AIR MONITORING - The OSHA Asbestos Standards specify required air monitoring in worksites with asbestos exposure. Refer to the Micromedex, Inc REGSLINK(R) Information System for more information.

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ASBESTOS

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5.0 CASE REPORTS

A. ADULT

1. A 44-year-old woman diagnosed with mesothelioma had been exposed to talc for over 12 years (Barnes & Rogers, 1984). Lung tissue revealed elevated levels of amosite.
2. A 76-year-old nonsmoking housewife with no direct occupational exposure to asbestos presented with pleural effusion and died of malignant mesothelioma, believed to have been acquired after "bystander" exposure from her husband who worked for 34 years as a machinist in a shipyard (Huncharek et al, 1989).
3. A 72-year-old male with known asbestos exposure presented with dyspnea on exertion and chest discomfort for about six months prior to admission. Computed tomography of the thorax revealed mild pleural thickening of the right upper thorax and severe pleural thickenings on the left interior and posterior thorax. Pleural biopsy demonstrated a diffuse fibrosis.
 - a. Six weeks later, the patient returned with progressive weakness, malaise, weight loss, BUN of 63 mg/dL, creatinine of 4.5/dL, potassium of 5.3 mmol/L, and phosphate of 6.2 mg/dL. Abdominal ultrasound revealed bilateral hydronephrosis which was confirmed with an MRI scan. Fibrosis was noted surrounding the distal abdominal aorta and proximal iliac arteries. Intraoperative procedures revealed retroperitoneal and peri-iliac fibrosis with encasement of the right and left ureters in the fibrotic process.
 - b. Lysis of the retroperitoneal fibrosis and periureteral adhesions was performed. The ureteral segment was found to have periureteral fibrosis, consistent with retroperitoneal fibromatosis with invasion of the right ureter; 36 months after discharge, no further progression of symptoms was observed (Moguire et al, 1991).

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6.0 TREATMENT

6.1 LIFE SUPPORT

- A. Support respiratory and cardiovascular function.

6.4 MONITORING

- A. Chest X-ray and pulmonary function tests should be monitored in asbestos-exposed patients.

6.5 INHALATION EXPOSURE

6.5.1 DECONTAMINATION

A. ACUTE EXPOSURE -

1. Most asbestos exposures are of a chronic nature, such that traditional first aid is not appropriate. In the event of a heavy ACUTE exposure -
2. INHALATION: Move patient to fresh air. Monitor for respiratory distress. If cough or difficulty breathing develops, evaluate for respiratory tract irritation, bronchitis, or pneumonitis. Administer oxygen and assist ventilation as required. Treat bronchospasm with beta2 agonist and corticosteroid aerosols.
3. Chest x-ray may be indicated.

B. CHRONIC/OCCUPATIONAL EXPOSURE -

1. OSHA mandates active medical surveillance programs in worksites where asbestos is present. Refer to the Micromedex, Inc REGSLINK(R) Information System for more information.
2. Institute aggressive "no smoking" policies for employees in such worksites. It has been shown that smoking increases the risk of developing cancer (Newhouse, 1983) by producing a synergistic effect between tobacco smoke and asbestos fibers (ATSDR, 1995).
3. Minimize exposure of the general populace by decreasing the use of asbestos and by substituting other products.
4. Abatement of asbestos in existing structures should be accomplished only by an EPA-certified contractor.

6.5.2 TREATMENT

A. SYMPTOMATIC/SUPPORTIVE CARE

1. ASBESTOSIS - Since there is no effective therapy for an established case of asbestosis, treatment is aimed at maintaining vital capacity and reducing respiratory work load

(Mossman & Gee, 1989).

2. Similar to other patients with chronic pulmonary diseases, treatment is aimed at supportive efforts and may include the following: vaccination against pneumococcal pneumonia and influenza, bronchodilator administration, adequate nutrition, home oxygen therapy, and rebreathing and exercise training. Pharmacological agents to limit the progression of fibrosis as yet have not been beneficial (Wagner, 1997).
3. MESOTHELIOMA - Neither surgery, chemotherapy, nor radiotherapy have been successful in producing remission of mesothelioma (Newhouse, 1983). Multimodal therapy has been employed to prolong disease-free intervals (Talcott & Antman, 1988).
4. PLEURAL PLAQUES - Plaques by themselves have little effect on pulmonary function and life expectancy, and do not produce complications that necessitate treatment (Dark & Pingleton, 1983; Jones et al, 1988).
5. PLEURAL EFFUSION - No therapy is necessary for this complication; however, close monitoring is mandatory to rule out mesothelioma and other possible causes (Dark & Pingleton, 1983).

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ASBESTOS

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7.0 RANGE OF TOXICITY

7.1 SUMMARY

- A. Statistical analysis indicates that low-level exposures or occupational exposure for under two years were not associated with increased mortality, but asbestosis has rarely been reported with intense exposure of only one day's duration.
- B. Carcinogenicity of asbestos fibers depends on mechanical stability, insolubility in aqueous solution, fiber strength, fiber diameter, and fiber geometry.

7.3 MINIMUM LETHAL EXPOSURE

- A. Using the presence of persistent, high-pitched rales in the basal portions of the lungs as criterion for the diagnosis of asbestosis, it was determined from a population of asbestos textile workers that less than 100 fiber-years of exposure (2 fibers/cc over a 50-year working period or 4 fibers/cc over a 25-year period) would cause the development of asbestosis in no more than 1 percent of the workers (ACGIH, 1991).
- B. Occasionally, asbestosis may develop fully in 7 to 9 years after exposure. Mesothelioma can occur after a short, intensive exposure; cases in children under 19 years of age indicate that the latent time period for development may be shorter than first estimated. Usually, however, asbestosis, pneumoconiosis, and mesothelioma develop 20 to 40 years after exposure (Hathaway et al, 1996).

7.4 MAXIMUM TOLERATED EXPOSURE

- A. The major route of exposure is inhalation of airborne fibers (ATSDR, 1990).
 - 1. Weil et al (1979) indicated via statistical analysis that low level exposures or occupational exposure for under 2 years were not associated with increased mortality.
 - 2. Development of asbestosis probably depends on a combination of asbestos dust concentration, fiber morphology, and length of exposure (Hathaway et al, 1996).
 - 3. Cigarette smoking is strongly implicated as a cocarcinogen among asbestos workers. Asbestos workers who smoke have approximately 15 times the risk of developing lung cancer compared to non-smoking asbestos workers (ACGIH, 1991; Hathaway et al, 1996; IARC, 19??).
- B. Oral exposure to asbestos may be experienced through drinking water, beer and other alcoholic beverages, and foods. This may be due to contamination, use of asbestos filters, or asbestos piping (ATSDR, 1990; Howe et al, 1989; McRae, 1988; Polissar et al, 1985).
 - 1. Such exposures have not generally been considered dangerous, although because of the long latent period to onset of asbestosis, several groups have been investigated (Anon, 1978; Howe et al, 1989; McRae, 1988).

2. Minor oral exposure occurs from ingestion of contaminated drinking water or after mucociliary clearance from the lungs, but the role, if any, of ingested asbestos as an etiologic agent is not known (ATSDR, 1990).
3. The US EPA proposed maximum contaminant level for asbestos in drinking water is 7 million fibers (larger than 10 microns in length) per liter (ATSDR, 1990).
4. Gastrointestinal tumors potentially caused by asbestos have only been statistically significantly increased in persons with occupational exposure (Anon, 1978). A possible synergistic effect of smoking and asbestos for cancers of the stomach, colon-rectum, and kidney has not been confirmed (ATSDR, 1990).

7.6 LD50/LC50

A. References: Lewis, 1996; RTECS, 1999

TCLo - (INHL) HUMAN: 1.2 fb/cc for 19Y-C --
pulmonary effects
TDLo - (IMPLANT) RAT: 750 mg/kg -- equivocal
tumorigenic agent

7.8 OTHER

A. GENERAL

1. ASBESTOS - The cancer-causing ability of asbestos seems to be related to fiber length, type, size, geometry, and insolubility in aqueous solutions (ACGIH, 1986; Brown et al, 1990; Churg et al, 1989; Gibbs, 1990; ILO, 1983; Lippman, 1988; McDonald et al, 1989; Mossman & Gee, 1989; Sebastien et al, 1989; Spurny et al, 1983). In order of toxicity, these fibers are crocidolite, amosite, and chrysotile.

B. SPECIFIC SUBSTANCE

1. CHRYSOTILE -

- a. Chrysotile and other amphiboles are not stable in acids, hydroxides, and living tissue (Spurny et al, 1983). Chrysotile is by far the most sensitive to these effects.
 1. Leaching of minerals from chrysotile will change various biological effects (Spurny et al, 1983). Leaching occurs naturally but slowly in human tissue. For example - the less magnesium, the less propensity to absorb albumin; when 50 percent of magnesium is removed, the hemolytic activity decreases; when 90 percent of magnesium is removed, the incidence of mesothelial tumors decreases substantially. When magnesium is leached from chrysotile by either acids or organic acids, both the cytotoxicity and hemolytic activity is decreased.
 2. With amosite or crocidolite, cytotoxicity and hemolytic activity are slightly enhanced rather than decreased by leaching.

C. OTHER TDLo/TCLo

1. AMOSITE -

- a. TCLo (INHL) RAT - 11 mg/m(3)/2 years-intermittent CARCINOGENIC (Lewis, 1992)
- b. TDLo (INTRAPLEURAL) RAT - 80 mg/kg CARCINOGENIC (Lewis, 1992)
- c. TDLo (SC) MOUSE - 2400 mg/kg/13 weeks-intermittent CARCINOGENIC (Lewis, 1992)

2. ANTHOPHYLITE -

- a. TCLo (INHL) RAT - 11 mg/m(3)/1 year-intermittent CARCINOGENIC (Lewis,

- 1992)
- b. TDLo (INTRAPLEURAL) RAT - 200 mg/kg NEOPLASTIC (Lewis, 1992)
3. ASBESTOS -
- a. TCLo (INHL) HUMAN - 1.2 fibers/mL/19 years-continuous PULMONARY (RTECS, 1995).
 - b. TD (INTRAPLEURAL) RAT - 100 mg/kg (Lewis, 1992)
 - c. TDLo (IP) RAT - 50 mg/kg (Lewis, 1992)
4. CHRYSOTILE -
- a. TCLo (INHL) HUMAN - 2.8 fibers/mL/5 years PULMONARY (RTECS, 1995)
 - b. TCLo (INHL) MAN - 400 million particles per cubic foot/1 year-continuous CARCINOGENIC, PULMONARY (Lewis, 1992)
 - c. TDLo (ORAL) RAT - 7100 mg/kg/39 weeks-continuous CARCINOGENIC (Lewis, 1992)
 - d. TCLo (INHL) RAT - 11 mg/m(3)/26 weeks-intermittent CARCINOGENIC (Lewis, 1992)
 - e. TDLo (SC) MOUSE - 2400 mg/kg/13 weeks-intermittent NEOPLASTIC (Lewis, 1992)
5. CROCIDOLITE -
- a. TCLo (INHL) RAT - 11 mg/kg/1 year-intermittent CARCINOGENIC (Lewis, 1992)
 - b. TDLo (IP) RAT - 100 mg/kg CARCINOGENIC (Lewis, 1992)
 - c. TDLo (IMPLANT) RAT - 200 mg/kg NEOPLASTIC (Lewis, 1992)
 - d. TDLo (INTRAPLEURAL) MOUSE - 200 mg/kg EQUIVOCAL TUMOR AGENT (Lewis, 1992)
6. TREMOLITE -
- a. TDLo (INTRAPLEURAL) RAT - 100 mg/kg EQUIVOCAL TUMORIGENIC AGENT, NEOPLASTIC (Lewis, 1992)

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8.0 KINETICS

8.1 ABSORPTION

A. INHALATION

1. The primary route of asbestos entry into the body is through inhalation (ATSDR, 1990).

B. ORAL

1. Ingestion of asbestos fibers can occur from drinking contaminated water or after mucociliary clearance from the lungs (ATSDR, 1990), but the cancer risk (if any) associated with this mode of entry has yet to be determined.
 - a. A case-control interview-based study conducted with 382 cancer patients and 462 controls from the Everett, Washington area found no convincing evidence for cancer risk from asbestos presumed to have been imbibed from a high concentration of chrysotile in the drinking water (Polissar et al, 1985).

C. DERMAL

1. Asbestos fibers may also lodge in the skin (ATSDR, 1990).

8.4 EXCRETION

8.4.4 OTHER

- A. Asbestos fibers thicker than 3 micrometers in diameter or longer than 100 mcm are either not inhaled or are rapidly cleared from the respiratory tract (IARC, 1985). On a weight basis, only a very small proportion of inhaled fibers is retained.
- B. When inoculated intrapleurally, the majority of asbestos fibers were cleared during the first 10 days (IARC, 1985). Subsequently, there was a very small elimination through the gut.
- C. In feeding experiments, almost all the asbestos fibers were eliminated in the feces (IARC, 1985).

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9.0 PHARMACOLOGY/TOXICOLOGY

9.2 TOXICOLOGIC MECHANISM

A. **CYTOTOXICITY** - The actual toxic mechanisms of the different asbestos fibers is not well understood.

1. Experimental animal studies have suggested a role for lipid peroxidation, adsorption of red blood cells on asbestos fibers, decreased calcium- and magnesium-activated ATPase activities, stimulated phosphatidylinositol turnover, activation of protein kinase C, and increased cytochrome C oxidase activity (Bissonnette et al, 1990; Goodglick et al, 1989; Goodglick & Kane, 1990; Elferink et al, 1989; HSDB, 1995; Iguchi & Kojo, 1989; Roney & Holian, 1989).
2. In vitro studies found that more than 20 mcg/mL of chrysotile can increase prostaglandin E2 production by macrophages and target cells and inhibit the cytotoxicity of rat alveolar macrophages (Bissonnette et al, 1990).
3. In vitro studies found that crocidolite fibers induce lipid peroxidation and disrupt the mitochondrial membrane potential in mouse macrophages (Goodglick & Kane, 1990; Goodglick et al, 1989). Hemolysis of human erythrocytes was attributed to the same mechanism (Iguchi & Kojo, 1989).
4. With asbestos exposure, polymorphonuclear leukocytes can generate hydrogen peroxide which causes hemolysis and injury to human pulmonary epithelial cells (Iguchi & Kojo, 1989; Kamp et al, 1989). Superoxide anion production has also been noted in asbestos-exposed guinea pig and human alveolar macrophages (Rom et al, 1987; Roney & Holian, 1989).
5. Iron was required for hydroxyl radical production in alveolar epithelial cells cultured with asbestos. Both cytotoxicity and DNA damage were dependent on the production of hydroxyl radicals (Kamp et al, 1995).
6. Chrysotile asbestos induced release of lactic dehydrogenase from rabbit peritoneal polymorphonuclear leukocytes and caused membrane damage and cytotoxicity (Elferink et al, 1989). With extracellular calcium, asbestos activated exocytosis and release of lysozymes and glucuronidase.
7. Asbestos fibers exerted a dose-dependent functional suppressive, rather than cytotoxic, effect on the natural killer (NK) effector cells, thus rendering the NK cells "paralyzed" once bound to their targets (deShazo et al, 1988; Robinson, 1989).
8. Studies with human breast carcinoma cells and human laryngeal carcinoma cells suggest an interaction between asbestos fibers and the normal mitotic process. After fiber penetration of the cell cytoplasm, a rearrangement of the cytoskeletal apparatus appears to occur. Internalization of fibers appears to lead to formation of giant multinucleated cells (Malorni et al, 1990).

B. **FIBROGENESIS** - The mechanisms that govern the fibrogenic effects of asbestos in the lungs

have not been completely elucidated. Two currently popular theories (not mutually exclusive) involve a central role of oxygen radicals generated by the asbestos fibers, versus induction of various growth factors and cytokines to mediate fibrosis (Brody, 1993).

1. With asbestos inhalation, alveolar macrophages accumulate at the area of fiber deposition (Mossman et al, 1990).
 2. With phagocytosis of the fiber, the activated macrophages produce a mixture of fibroblast growth factors, chemoattractants, fibronectin, prostaglandins, procoagulants, leukotriene B4, lysozomal enzymes, active oxygen metabolites, tumor necrosis factor-alpha, and interleukin 1 (ATSDR, 1990; Bissonnette et al, 1990; Callahan et al, 1990; Dark & Pingleton, 1983; Elferink et al, 1989; Garcia et al, 1989; Goodglick et al, 1989; Goodglick & Kane, 1990; Hayes et al, 1988; HSDB, 1995; Iguchi & Kojo, 1989; Kagan, 1988; Mossman et al, 1990; Roney & Holian, 1989; Schwartz et al, 1989; Ljungman et al, 1994).
 3. Lung injury can be induced by an asbestos-related increase in neutrophils which release a collagenase and neutrophil chemotactic factors (Delclos et al, 1989; Garcia et al, 1989; Hayes et al, 1988; Mossman & Gee, 1989).
 4. These inflammatory mediators incite widespread tissue destruction, granuloma formation, and pulmonary fibrosis (ATSDR, 1990; Callahan et al, 1990; Chang et al, 1988; Dark & Pingleton, 1983; Garcia et al, 1989; Hayes et al, 1988; Kagan, 1988; Schwartz et al, 1989).
 5. Once inside the macrophages, the fibers may be coated with a mucopolysaccharide and iron matrix, thus forming the drumstick configuration of the ferruginous asbestos bodies (ATSDR, 1990; Dark & Pingleton, 1983). In asbestosis, coated fibers may be much fewer than uncoated fibers which exert the most damage (Dark & Pingleton, 1983).
 6. Because the fibers concentrate in the lower lung fields, fibrosis tends to occur first in the lung bases; pleural effects are generally confined to the lower two-thirds of the thorax.
 7. Plaques are formed when sharp fibers (such as anthrophyllite) penetrate into the pleura during breathing or via the lymphatic system (Dark & Pingleton, 1983).
 8. Asbestos fibers can also penetrate to the terminal bronchioles and elicit a fibrogenic response upon entry into the peribronchiolar space (ATSDR, 1990).
 9. The pneumoconiotic reaction appears to be more closely related to the surface area as opposed to the number of retained fibers per gram of lung tissue (Becklace, 1991).
- C. CARCINOGENESIS - The mechanism(s) by which asbestos can induce cancer is not known. It is unclear whether or not asbestos can induce carcinogenesis by initiating a heritable genetic change and promoting this with proliferative and genotypic changes (Mossman et al, 1990).
1. The reactive oxygen metabolites produced in asbestos-induced lipid peroxidation can cause mutations, DNA strand breaks, chromosomal breaks, nuclear changes, and epigenetic changes (Goodglick & Kane, 1990).
 2. Because 144 patients with asbestos-related mesotheliomas had important differences from the epidemiological pattern of asbestos-related bronchogenic cancer, it was suggested that asbestos may not act as a complete carcinogen, but rather as a promoter (Browne, 1983).
 3. Longitudinal and cross-sectional data from a brake manufacturing plant also suggest the irritant role of asbestos (Parnes, 1990).
 4. Asbestos absorbs carcinogens like benzo(a)pyrene and catalyzes the oxidation of weak to potent carcinogens (Dunn, 1989). Hydrogen peroxide in cigarette smoke and asbestos may induce DNA strand breaks via a hydroxyl radical dependent mechanism.
 5. The development of mesothelioma seems to be related to the length and diameter of fibers and to prolonged exposure, although there have been reports with very minimal asbestos exposure (Dunn, 1989). Unlike bronchogenic carcinoma, there is no association

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10.0 STANDARDS/LABELS

10.1 STANDARDS

10.1.1 WORKPLACE STANDARDS

- A. ACGIH-TLV (all forms): 0.1 f/cc TWA; no STEL (ACGIH, 2001) Note: (f) Fibers longer than 5 microns and with an aspect ratio equal or greater than 3:1 as determined by the membrane filter method at 400-450X magnification (4-mm objective) phase contrast illumination.
 - 1. Notation(s):
 - a. Skin Notation: Not Listed
 - b. Carcinogenicity: Confirmed Human Carcinogen
 - 2. Molecular weight: Not applicable
 - 3. TLV Basis - Critical Effect(s): Asbestosis; cancer
- B. OSHA PEL: Listed (OSHA, 1997a)
 - 1. There is no specific value listed for asbestos at 29 CFR 1910.1000 Table Z-1.
 - a. Note: OSHA standards to regulate occupational exposures to asbestos may be found at 29 CFR 1910.1001. The 8-Hour TWA is less than 0.1 fiber/cc with an excursion limit of 1.0 fiber/cc (30 min average).
- C. OSHA List of Highly Hazardous Chemicals, Toxics and Reactives: Not Listed (OSHA, 1997)
- D. NIOSH VALUES: (NIOSH, 1999)
 - 1. REL: Refer to Appendix A and Appendix C in the NIOSH Pocket Guide(TM) on TOMES Plus(R) for more information.
 - a. Skin Notation: Not Listed
 - 2. IDLH VALUE: Not Yet Determined
 - a. NIOSH considers this substance to be a potential occupational carcinogen.
- E. AIHA WEEL VALUE: Not Listed (AIHA, 1996)

10.1.2 ENVIRONMENTAL STANDARDS

- A. SARA TITLE III
 - 1. EHS (EXTREMELY HAZARDOUS SUBSTANCES) LIST: Not Listed (EPA, 1997f)
 - 2. SECTION 313: Listed (as Asbestos (friable)) (EPA, 1997g)
 - a. Effective Date: 1/1/87
- B. CERCLA; HAZARDOUS SUBSTANCES and REPORTABLE QUANTITIES: Listed (EPA, 1997e)
 - 1. Statutory RQ (Reportable Quantity):
 - a. 1* pound - (1* Indicates that the 1-pound RQ is a CERCLA statutory RQ).
 - b. Codes: Listed
 - 1. 2 - Indicates that the statutory source for designation of this hazardous

substance under CERCLA is CWA Section 307(a). 3 - Indicates that the statutory source for designation of this hazardous substance under CERCLA is CAA Section 112.

2. Final RQ (Reportable Quantity):
 - a. 1 pound (0.454 kilogram)
 - b. Notes: Listed
 1. The RQ for asbestos is limited to friable forms only.
 - c. Final RQ Category: X
- C. RCRA HAZARDOUS WASTE NUMBER: Not Listed (EPA, 1997; EPA, 1997a; EPA, 1997b; EPA, 1997c; EPA, 1997d)
- D. TSCA INVENTORY: Listed (LOLI, 1999)
- E. AIHA ERPG VALUES: Not Listed (AIHA, 1996)
- F. DOT List of Marine Pollutants: Not Listed (DOT, 1997a)

with smoking.

- D. There is growing interest in the possible role of free radicals in asbestos-mediated carcinogenesis. Peroxides enhance the activity of asbestos in causing DNA damage (Mahmood et al, 1993; Mahmood et al, 1994). Peroxides react with ferrous ion complexed to asbestos particles to generate free radicals and DNA damage (Ghio et al, 1994).
- E. Mononuclear peripheral leukocytes from patients with lung cancer were more active for generating reactive oxygen species in the presence of asbestos than were cells from patients without cancer. The level of reactive oxygen generation was inversely correlated with one-year survival rates in these patients (Nyberg et al, 1994).
- F. Asbestos can induce expression of c-fos and c-jun oncogenes in rat pleural mesothelial cells; crocidolite was more active than chrysotile for this effect, as it is for induction of mesothelioma (Heintz et al, 1993).

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11.0 PHYSICOCHEMICAL

11.1 PHYSICAL PARAMETERS

11.1.1 PHYSICAL CHARACTERISTICS

- A. Asbestos is a generic name for a class of naturally occurring, hydrated, fibrous silicates. In general, asbestos fibers are white, gray, green, or brown fibers, have exceptional tensile strength, are moldable, and are relatively inert chemically. They are incombustible in air and separate into filaments. Asbestos is divided into two groups (Budavari, 1996; ITI, 1988; Lewis, 1993, Lewis, 1998; Sittig, 1991):
1. Serpentine asbestos is the mineral chrysotile, a magnesium silicate, with strong, flexible fibers. It is possible to spin the longer serpentine fibers. Serpentine or chrysotile asbestos (white asbestos) is the most common form of asbestos.
 2. Amphibole asbestos includes various silicates of magnesium, iron, calcium, and sodium. The fibers of this group are generally brittle and cannot be spun, but they are more resistant to chemicals and heat than serpentine asbestos. Subdivisions of amphibole asbestos include anthophyllite, amosite, actinolite, tremolite, and crocidolite (blue asbestos).

11.1.5 OTHER

- A. HEAT CONDUCTIVITY: conducts heat poorly (Lewis, 1998)

11.2 CHEMICAL PARAMETERS

11.2.2 REACTIVITY

- A. Asbestos has high tensile strength, relative resistance to acid and temperature, and varying textures and degrees of flexibility (ATSDR, 1990). It does not evaporate, dissolve, burn, or undergo significant reactions with other chemicals; thus, it is nonbiodegradable and environmentally cumulative (ATSDR, 1990).
- B. Chrysotile asbestos is not stable in acids, hydroxides, and living tissue (Budavari, 1996; Spurny et al, 1983).

11.2.3 SOLUBILITY

A. SOLUBILITY IN WATER

1. Asbestos as a class is virtually insoluble (Lewis, 1998).

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12.3 CONSULTANTS

- A. The above information is generic for the compound. For further product specific information, consult manufacturer. In an emergency, contact CHEMTREC at 1-800-424-9300 or 703-527-3887 if outside the continental U.S.
- B. Immediately notify the National Response Center (1-800-424-8802) if a release of a reportable quantity of a hazardous substance to the environment has occurred.
- C. Assistance with identifying asbestos in public or private buildings:
 1. On May 27, 1982 the EPA required all public and private elementary and secondary schools to identify friable asbestos used in their buildings. Records of findings must be kept by the school, and if friable asbestos is found, the school must notify its employees and PTA groups.
 2. Schools (or other business or private individuals) may contact their regional EPA office for information regarding asbestos materials, availability of analysis, and risk evaluation. Regional asbestos coordinators (Revised 12/91) are listed below:

SCHOOLS

EPA Region I
CT, MA, ME, NH, RI, VT
Air & Management Division
JFK Federal Building
Boston, MA 02203
(617) 565-3835
EPA Region II
NJ, NY, PR, VI
Woodbridge Avenue
Raritan Depot, Building 5
Edison, NJ 08837
(908) 321-6671

EPA Region III
DC, DE, MD, PA, VA, WV
841 Chestnut Street
Philadelphia, PA 19107
(215) 597-3160

EPA Region IV
AL, FL, GA, KY, MS, NC, SC, TN
345 Courtland Street NE
Atlanta, GA 30365
(404) 347-5014

EPA Region V
IL, IN, MI, MN, OH, WI
230 S Dearborn Street
Chicago, IL 60604
(312) 886-6003

EPA Region VI
AR, LA, NM, OK, TX
1445 Ross Avenue
Dallas, TX 75202
(214) 655-7244

EPA Region VII

BUSINESSES/RENOVATION (NESHAP Coordinators)

EPA Region I
CT, MA, ME, NH, RI, VT
Air & Management Division
JFK Federal Building
Boston, MA 02203
(617) 565-3265
EPA Region II
NJ, NY, PR, VI
Air & Waste Management
Division
26 Federal Plaza N
New York, NY 10278
(212) 264-6770

EPA Region III
DC, DE, MD, PA, VA, WV
841 Chestnut Street
Philadelphia, PA 19107
(215) 597-6550

EPA Region IV
AL, FL, GA, KY, MS, NC, SC, TN
345 Courtland Street NE
Atlanta, GA 30365
(404) 347-5014

EPA Region V
IL, IN, MI, MN, OH, WI
230 S Dearborn Street
Chicago, IL 60604
(312) 886-6793

EPA Region VI
AR, LA, NM, OK, TX
1445 Ross Avenue
Dallas, TX 75202
(214) 655-7223

EPA Region VII

IA,KS,MO,NE
726 Minnesota Avenue
Kansas City, KS 66101
(913) 551-7623
EPA Region VIII
CO,MT,ND,SD,UT,WY
999 18th Street
Suite 500
Denver, CO 80202
(303) 293-1442
EPA Region IX
AS,AZ,CA,GU,HI,NV
Northern Marianas,TT
75 Hawthorne Street
San Francisco, CA 94105
(415) 744-1087
EPA Region X
AK,ID,OR,WA
1200 Sixth Avenue
Seattle, WA 98101
(206) 553-4762

IA,KS,MO,NE
726 Minnesota Avenue
Kansas City, KS 66101
(913) 551-7623
EPA Region VIII
CO,MT,ND,SD,UT,WY
999 18th Street
Suite 500
Denver, CO 80202
(303) 293-1442
EPA Region IX
AS,AZ,CA,GU,HI,NV
Northern Marianas,TT
75 Hawthorne Street
San Francisco, CA 94105
(415) 744-1137
EPA Region X
AK,ID,OR,WA
1200 Sixth Avenue
Seattle, WA 98101
(206) 553-1757

3. GERMANY: Contact the local Gesundheitsamt or Technischer Ueberwachungs-Verein for information.

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- D. Specialty Board: Industrial/Chemicals Refer to the TOMES EDITORIAL BOARD section for more information.