REVIEW OF LITERATURE

"...... But there is no possible knowledge, which arrives not from a pre-existent knowledge, and that very demonstrable"

W. Harvey
1. ASBESTOS: PHYSICO-CHEMICAL PROPERTIES AND ITS TOXICITY

Asbestos is a generic name used for a group of naturally occurring hydrated mineral silicates that crystallize in a fibrous habit, and can be classified either as serpentine or amphibole. Chrysotile is the only member of the serpentine group, that accounts for approximately 93% of the asbestos produced and used worldwide. It is a pliable, curly fiber made up of bundles of smaller fibrils. These bundles are comprised of overlapping sheets of silica and brucite (Mg (OH)\textsubscript{2}) which resemble concentric, scroll-like tubes (Yada, 1967). The main commercial amphiboles are crocidolite and amosite. Three other amphibole types—anthophyllite, actinolite, tremolite are not commercially exploited but can contaminate other commercial mineral deposits (Skinner et al., 1988). Crocidolite, a straight rod-like fiber, the principal amphibole of economic and health significance, is made up of parallel chains of silica tetrahedra separated by bands of cations. These well-known asbestos minerals have different fibrous properties and chemical formulae (National Research Council, 1984; World Health Organization, 1986) (Table 1).

The chemical make up of each fiber type is complex, and fibers acquire a variety of trace metals and organic compounds during mining and processing. The unique physico-chemical features of asbestos fibers, namely their strength, resistance to heat and chemicals, flexibility, durability and lower cost compared to man-made mineral fibers make them...
Table 1
Commercial Asbestos and Formulae.

<table>
<thead>
<tr>
<th>Mineral</th>
<th>Mineral Group</th>
<th>Chemical Formula</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>Chrysotile</td>
<td>Serpentine</td>
<td>$(\text{MgFe})_6(\text{OH})_8\text{Si}<em>4\text{O}</em>{10}$</td>
<td>White asbestos—the most commonly used variety</td>
</tr>
<tr>
<td>Riebeckite</td>
<td>Amphibole</td>
<td>$(\text{Na}_2\text{Fe}_2\text{Fe}_3(\text{OH})_2\text{Si}<em>8\text{O}</em>{22}$</td>
<td>Blue asbestos—Extensively used.</td>
</tr>
<tr>
<td>Anthophyllite</td>
<td>Amphibole</td>
<td>$(\text{MgFe})_7(\text{OH})_2\text{Si}<em>8\text{O}</em>{22}$</td>
<td>Usually a low quality asbestos. No longer commercially used. Present as a contaminant in amosite and in some chrysotile and talc deposits</td>
</tr>
<tr>
<td>Amosite</td>
<td>Amphibole</td>
<td>$\text{Mg}_7(\text{OH})_2\text{Si}<em>8\text{O}</em>{22}$</td>
<td>Brown asbestos. Still extensively used.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\text{Fe}_7(\text{OH})_2\text{Si}<em>8\text{O}</em>{22}$</td>
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</tr>
<tr>
<td>Actinolite</td>
<td>Amphibole</td>
<td>$\text{Ca}_2\text{Fe}_5(\text{OH})_2\text{Si}<em>8\text{O}</em>{22}$</td>
<td>Not commercially used. Common contaminant of amosite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\text{Ca}_2\text{Mg}_5(\text{OH})_2\text{Si}<em>8\text{O}</em>{22}$</td>
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especially attractive to industries. It has over 1000 commercial uses as it is currently incorporated into cement construction materials (roofing, shingles and cement fibers), friction materials (brake linings and clutch pads), jointings and gaskets, asphalt coats and sealings, and other similar products.

Various physico-chemical properties of mineral fibers—fiber type, fiber size, aspect ratio, aerodynamic radius, density of mineral particles, chemical composition, deposition, dissolution, migration, specific surface sites and surface charges are considered to be primary factors of the importance in the biological reactivity of mineral fibers and their toxicity (Table 2) (Light & Wei, 1977; Frank et al., 1979; Palekar et al., 1979; Chamberlain et al., 1979; Stanton et al., 1981; Kaw et al., 1982; Woodworth et al., 1982; Pott et al., 1983; Hesterberg et al., 1987). Exposure to asbestos fibers has been associated with the development of malignant (bronchogenic carcinoma, mesothelioma) and non-malignant (asbestosis) diseases of the lung (Mossman & Gee, 1989). In recent years many studies have been conducted to elucidate the mechanisms involved in these seemingly unrelated pathological tissue reactions and to determine the fiber characteristics essential for the toxic activities of asbestos (Beck & Bignon, 1985). These studies have led to two major hypotheses. According to the one hypothesis, fiber size (length or diameter) is the key factor determining the degree of toxicity (Stanton et al.,
<table>
<thead>
<tr>
<th>Factors</th>
<th>Consequence of influence</th>
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<tr>
<td>Size, aspect ratio and density</td>
<td>Transport, respirability, clearance, phagocytosis translocation</td>
</tr>
<tr>
<td>Chemical composition and structure</td>
<td>Leaching of ions, solubility, persistence</td>
</tr>
<tr>
<td>Surface texture (roughness)</td>
<td>Cell-particle adhesion, cell wall distortion</td>
</tr>
<tr>
<td>Charge density, distribution</td>
<td>Cell-particle adhesion, adsorption of ionic species.</td>
</tr>
<tr>
<td>Surface adsorption</td>
<td>Transport of foreign species, adsorption of lipids and proteins, changes in bioavailability of essential components</td>
</tr>
<tr>
<td>Reactive surface sites</td>
<td>Acid-base, redox, electron transfer reaction</td>
</tr>
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1981). The other hypothesis states that surface properties, such as surface charge is the most important determinant of fiber toxicity (Bignon & Jaurand, 1983). There is indeed evidence supporting both hypotheses and it seems reasonable to speculate that both factors are important (Beck & Bignon, 1985).

Besides the physical characteristics of mineral fiber, the chemical composition and crystalline structure of the fiber also play an important role in the toxicity (Craighead et al., 1980; Woodworth et al., 1982). A number of trace metals including Ni, Cr, Sb, and Co are associated with asbestos fibers which have been implicated as one of the causative factor of asbestos related diseases (Shugar, 1979; Barbeau et al., 1985). Some workers have been reported that trace metals associated with asbestos fibers are involved in its co-carcinogenic behaviour and can influence the metabolism of polynuclear aromatic hydrocarbons, the major components of cigarette smoke and combustion materials (Dixon et al., 1970; Thomson et al., 1974).

Lung damage due to solubility of toxic elements such as magnesium or silica have been reported by Jaurand et al (1977). Recently, Morgan and Holmes (1986) have demonstrated that solubility of both fibrous and non-fibrous dusts in the lung are considered to be an important factor, which may have an immediate cytotoxic effect upon cells of the lung but are unlikely to induce long term pathological alterations. It is established that chrysotile is unstable in water, physiological saline or acidic medium as it rapidly
loses its Mg from the fiber structure, while amphiboles are more stable in the physiological media (Thomassin et al., 1976; Hodgson & Jones 1986). The magnesium content of chrysotile is also related to toxicity and hemolytic activity (Harington et al., 1974; Light & Wei, 1983). Dissolution of silicic acid from the dust in physiological fluids could also be attributed to some of the toxic manifestations produced by chronic inhalation of noxious silicate dust (Rahman et al., 1975 & 1977a). It was also observed that silicic acid leached out from silicate dust could be implicated as an acute factor in the lysis of erythrocytes (Rahman et al., 1974), release of lysosomal enzymes (Rahman et al., 1976), and interaction with constituents of biomembranes (Rahman et al., 1979). Recently, Singh and Rahman (1987) have reported that silicic acid induced lipid peroxidation and hemolysis in red blood cells (RBCs) by two separate mechanisms.

Although many different types of mineral fibers produce similar diseases there may still be some role of fiber composition in determining pathogenicity (Craighead et al., 1980; Reiss et al., 1980; Woodworth et al., 1982). One accepted role of composition is as a determinant of fiber durability in vivo, but the nature of any interaction between the fiber and cell at the molecular level must also depend on the chemistry of the fiber surface. Physical or chemical interactions between fibers and cells must occur before any pathogenic activities are expressed.
Two types of active sites on the fiber surface may occur, one conceivably acting as a proton donor and the other functioning as a proton acceptor (Born & Prigogine, 1979). It has been suggested that the chemical reaction on the silica surface with water molecules results in the formation of hydroxyl groups. Furthermore, a change in the polarity of the Si-O bond could be responsible for an increase of the ionic character of surface hydroxyl group (Prigogine, 1974). The hydrated surface is capable of hydrogen bonding with water, other biological macromolecules and damaging membrane bound enzymes (Prigogine, 1974; Kandaswami et al., 1986). It is conceivable, therefore, that the intrinsic properties of the surface lattice of the amphibole and serpentine, the two different types of asbestos, may be involved in their bioreactivity.

The surface electrostatic potential of the mineral fibers can also play an important role in the cell-particle interactions. It results from ionic charges on the surface of asbestos, due to surface structural defects, ionization of surface groups or adsorption of ions from the medium (Mossman et al., 1983; Jolicoeur & Poisson, 1987). Recently, it was hypothesized that a fibronectin-mediated mechanism is involved in the interactions between amphibole fibers and cell surfaces (Brown et al., 1991).

Several biological macromolecules and enzymes are known to be adsorbed on the surface of asbestos and affect the physiological functions of the cells (Mossman et al., 1983; Fisher et al., 1987; Jolicoeur & Poisson, 1987). The
demonstrated ability of mineral particles to adsorb numerous types of molecular species suggests that these particles can act as carriers of foreign molecules into the various substructures of biological systems (Jolicoeur & Poisson, 1987). The adsorption of polynuclear aromatic hydrocarbons (PAHs) on various types of asbestos and related minerals have attracted considerable interest in relation to asbestos-PAHs toxicity synergy (Berry et al., 1972; Meurman et al., 1979). On the basis of the adsorption phenomenon, an alternative mechanism of carcinogenesis is proposed in which asbestos slows down normal cellular metabolism of carcinogens in vitro and leads to increased cellular retention of the carcinogens (Kandaswami et al., 1986). The foreign molecules adsorb reversibly on the surface of asbestos and do not undergo any bond breaking reactions in their adsorbed state. It has been reported that chemical adsorption is required for catalytic reactions such as electron transfer (Hauffe & Wolkenstein, 1969). It appears that an initial biological interaction with asbestos involves the transfer of metastable electrons (Fisher et al., 1987). This electron transfer process may be facilitated by the positive charge on chrysotile asbestos and coulombic interaction with negatively charged cell surface (Fisher et al., 1987).

A burgeoning area of interest is the role of active oxygen species (AOS) in asbestos induced cell damage and proliferation which has solved a question to a lesser extent that how dissimilar physico-chemical characteristics of
various types of asbestos relate to their common ability to cause cell damage and diseases of the lung. The importance of AOS in contributing to asbestos-associated cytoxicity has been indicated by several studies (Mossman et al., 1986a; Donaldson et al., 1986; Shatos et al., 1987; Kamp et al., 1992). Several workers have been reported that asbestos appears to generate damaging AOS from target cells of disease as well as from inflammatory cells during the phagocytic process (Donaldson & Cullen, 1984; Goodglick & Kane, 1986; Hansen & Mossman, 1987). The latter cell types may act as mediators of disease by releasing AOS which then affect other cell types. The work from several laboratories shows that cell interaction is not necessary for production of AOS from asbestos fibers. For example, fibers like chrysotile or crocidolite in cell free solutions of H$_2$O$_2$ or physiological saline spontaneously generate superoxide (O$_2^-$) and hydroxyl radicals (OH') (Weitzman & Graceffa, 1984; Ebenhardt et al., 1985). These reactions generating AOS appear to be driven by iron on the surface of fibers as preincubation of fibers with iron chelators diminishes these reactions (Shatos et al., 1987). For example, iron II salts can react with oxygen in an aqueous environment to yield O$_2^-$ and OH' radicals directly (i.e. Fe$^{2+}$ + O$_2$ -> Fe$^{3+}$ + O$_2^-$) (Wong et al., 1981). Furthermore, iron catalyzes the modified Haber-weiss (Fenton-like) reactions producing the highly reactive OH' radicals (McCord & Wong, 1979). Brown (1987) has reported the catalytic role of iron in asbestos-induced lipid peroxidation and DNA strand breakage. Moreover, the
chelation of iron by deferoxamine ameliorates both the cytotoxicity of fibers (Goodglick & Kane, 1986; Shatos et al., 1987), and their ability to cause lipid peroxidation in membrane preparations (Gulumian et al., 1983; Weitzman & Weitberg, 1985). The crocidolite (21.5%) and amosite (26.6%) are primarily iron-containing asbestos types while the iron content of UICC chrysotile is only 1.9% as determined by neutron activation analysis (Wydler et al., 1988). It presumes that in the case of chrysotile other factors like Mg content and surface charges are also involved. Gulumian and Kilroe-Smith (1987) have shown that Mg$^{2+}$, Mn$^{2+}$ and Ca$^{2+}$ ions did not produce any significant effect on lipid peroxidation in the presence or absence of crocidolite. They concluded that it is the iron in the crocidolite that is responsible for the latter's ability to enhance lipid peroxidation. Moreover, lipid peroxidation is further enhanced upon addition of NADPH and asbestos; however, crocidolite being a more potent stimulus than chrysotile at similar concentrations (Fontecave et al., 1987; Wydler et al., 1988). These studies clearly indicate that iron derives reactions favouring the production of active oxygen species and subsequent cytotoxicity to cells. Recently, it has been reported that iron can be mobilized from asbestos in the cell by low molecular weight chelators and ascorbate (Lund & Aust, 1990). If this occurs, it may have deleterious effects since this could result in deregulation of normal iron metabolism by proteins within the cell result-
ing in iron catalyzed oxidation of biomolecules.

Active oxygen species generated upon phagocytosis of fibers by alveolar macrophages or by direct interaction of "target" cells with asbestos cause alterations in normal cell differentiation, e.g., increases in collagen biosynthesis, which may contribute to lung disease (Mossman et al., 1989). A common feature of all asbestos-induced diseases is an early and often sustained inflammatory response associated with the influx of macrophages, polymorphonuclear leukocytes and lymphocytes. Free radicals of oxygen have also been implicated in the inflammation (McCormick et al., 1981; Cerutti & Trump, 1991), fibrosis (Langer et al., 1979) and in the promotion of carcinogenesis of the lung (Copeland, 1983; Gabrielsson et al., 1986; Trush & Kensler, 1991). It is, therefore, interesting to note that asbestos is an inflammatory, fibrotic and carcinogenic agent (Mossman et al., 1990).

It is evident from the above studies that the generation of oxygen free radicals by asbestos might explain the increased pathogenic potential in asbestos associated diseases of respiratory tract. Therefore, the studies on the role of antioxidants against the free radical-mediated processes induced by asbestos may be very important, towards the prevention of the increased risk of various malignancies and asbestosis a non-malignant but progressive and restrictive lung disease caused by occupational and environmental exposure of asbestos fibers.

Finally, due to many crystalline and surface imperfec-
tions of naturally occurring minerals, the surface of mineral particles must be viewed as comprising a variety of sites which could be described in terms of their morphology, electrostatic charges, acid-base properties, redox properties, etc. Some of these sites could exhibit catalytic activity to initiate or promote chemical processes leading to toxicity manifestations.

Thus, the foregoing overview of physico-chemical properties of mineral particles, their stated interactions with biological macromolecules may comprise the main primary effects responsible for asbestos-induced toxicity.

2. HEALTH HAZARDS ASSOCIATED TO ASBESTOS EXPOSURE

Asbestos fibers in ores are not respirable until released and made airborne during mining, processing and transportation of the mined deposits. Once liberated, asbestos persists for an unknown length of time and contaminate both the working and non-working environment, air, water and food derived either from natural or industrial source (National Research Council, 1984). It has now been amply demonstrated that prolonged periods of inhalation of asbestos fibers of respirable size can lead to a number of toxic manifestations ranging from simple inflammatory reactions, to pulmonary fibrogenesis known as asbestosis, or even to carcinogenesis (Selikoff et al., 1980; Mossman, 1988; Mossman et al., 1990). Two major types of malignancies which are frequently found in occupationally exposed
asbestos workers are mesothelioma and bronchogenic carcinoma. Mesothelioma, a tumor of the serosal cells, lining the pleural and peritoneal cavities, is an extremely rare cancer in the general population but can account for as many as one in thirty of the malignancies found in asbestos workers (Selikoff et al., 1980). The second type of cancer in asbestos workers is bronchogenic carcinoma, a tumor of the epithelial cells lining the upper airways. However, some reports also describe high incidences of cancer of the gastrointestinal tract, larynx, kidney, pancreas, ovary and lymphatic system in certain asbestos exposed cohorts (Doll & Peto, 1987). Various known factors associated with the development of asbestos-mediated pulmonary disorders are:

i) nature of dust particles

ii) site of dust deposition in the respiratory tract

iii) the amount of dust deposited in the lung

iv) its exposure period, and

v) individual idiosyncrasy and immunological status

The various lung pathological disorders and/or diseases due to exposure of asbestos dusts to the respiratory system are discussed below with special reference to their toxic effects.

Asbestosis

Asbestosis is a chronic interstitial lung disease produced as a result of inhalation of asbestos over a long period of time (i.e. about 10-20 years after first exposure). Asbestosis is not the generic term for all
diseases associated with asbestos dust exposure but is reserved for the specific pathological entity of parenchymal fibrosis of the lung (Michael & Chissick, 1979). The pulmonary fibrosis in human is progressive with coalescing fibrotic lesions involving a large portion of the lung which reveals extensive reconstriction and coalescence of the alveoli in later stages (Becklake, 1976; Craighead & Mossman, 1982; Lee, 1985). The onset of the disease is marked by dyspnoea on exertion, nonproductive cough, rales at the lung bases and bronchi, and in advanced cases finger clubbing is also observed (Michael & Chissick, 1979; Selikoff et al., 1980). The working capacity of the workers diminished with the advancement of disease. The pulmonary fibrosis is characterized by (1) permanent alterations or destruction of alveolar architecture, (2) collagenous stromal reaction of moderate to mixed degree, (3) and permanent scarring of the tissue. The clinical, radiological and other signs on which the diagnosis is based are non-specific and subject to wide variations in interpretation (Acheson & Gardner, 1980). Asbestosis is dose-related, that is very high exposure could produce the disease in a short time, but low exposure may take more than a working life time to cause it (Acheson & Gardner, 1980; Casey et al., 1981). All types of asbestos can cause asbestosis (Acheson & Gardner, 1979), but chrysotile seems to be more fibrogenic than amphiboles (Davis et al., 1978).
Pulmonary fibrosis is of two types, that is diffuse and solid fibrosis (Gough, 1965). The diffuse form shows cystic areas of varying sizes, depending on whether the smaller air passages or large bronchi are dilated. The distribution is not extensive and the changes are not uniform, thus making it different from the predominantly peripheral changes of idiopathic interstitial fibrosis. On the other hand, the solid form of fibrosis may reach several centimeters in diameter and may occur in any part of the lung. Although asbestos exposure has been clearly associated with the development of a progressive fibrotic lung disease (Becklake, 1976; Craighead & Mossman, 1982), the mechanism(s) by which asbestos fibers induce lung fibrosis remains poorly defined. However, chemical and biochemical changes induced in the lung during the development of experimental asbestosis were studied with a view to elucidate the molecular mechanisms of asbestos toxicity (Rahman et al., 1977a & b; Misra et al., 1978). These studies, in consistence with other reports (Mossman & Gee, 1989) suggest that asbestosis can begin as a small airway disease, with the deposition of dust and collagen in the wall of peripheral airways. A characteristic response in animals, like-wise in human is an increase in lung collagen content. The development of reticulin fibrosis in animals with the accumulation of collagen and mucopolysaccharides alongwith abolition of lysosomal latency indicated a parallel relationship between lysosomal damage and fibrosis (Viswanathan et al., 1973a).
It has been suggested that fibrosis of lung involves the interaction between pulmonary alveolar macrophages (PAM) and lung fibroblasts (Allison et al., 1977; Reiser & Last, 1979; Churg, 1982; Lugano et al., 1984; Warheit et al., 1986). Briefly, this hypothesis suggests that asbestos fibers on reaching the alveolar surfaces, are ingested by macrophages, which represent the best defense against air pollutants via the mucociliary clearance (Clerici et al., 1986), but are promptly killed by cytotoxic effects of fibers. More macrophages entering the area also die and release of some fibrogenic factors occurs which stimulates the fibroblasts to increase collagen synthesis which eventually hyalinizes (Lemaire et al., 1986). In asbestosis, lung becomes fibrosed or scarred as a result of prolonged inhalation of asbestos fibers. The fine fibers once down in the lung, are not readily removed. In fact, they damage the scavenger cells. Unfortunately, scar formation in the lung destroys useful lung tissue at the fore end of the smallest bronchial tubes, the place where the lung transfers oxygen into the blood stream and ultimately impairs the lung's ability to take up oxygen. This leads to the patients becoming short of breath and as the disease progresses, may be responsible for their deaths.

Recently, it was reported that pulmonary fibrosis in asbestos insulation workers is associated with lung cancer (Browne, 1986; Rudle, 1987; Davis & Cowie, 1990).

Recent evidence suggests that active oxygen species (AOS) is the causative agent of both asbestosis and other
asbestos related malignancies (Rahman & Casciano, 1985; Mossman et al., 1986b & 1990). The generation of oxygen free radicals from cells of the immune system, specifically polymorphonuclear leukocytes and macrophages after a number of toxic insults by asbestos fibers have been very well documented to be associated with the development of inflammatory responses in the lung (Mossman et al., 1987). In an inhalation model of rapid onset asbestosis, osmotic pumps containing polyethylene glycol (PEG)-conjugated catalase, an enzyme scavenging H$_2$O$_2$, were implanted subcutaneously into rats before they were exposed to crocidolite for 20 days (Mossman et al., 1986c). This procedure boosted the levels of catalase in the sera and lungs of these animals and ameliorated both the inflammation and the severity and extent of fibrotic lesions that normally develop after inhalation of asbestos. Recently, Roney & Holian (1989) have suggested that chrysotile asbestos stimulates production of superoxide anions by stimulating phospholipase 'C' to activate protein kinase 'C'. Thus, in alveolar macrophages obtained from guinea pigs, agonist stimulation of superoxide anion production by chrysotile is achieved via activation of the phospholipase 'C' pathway (Holian, 1986). In this pathway, an occupied receptor can activate phospholipase 'C' through a pertussis toxin inhibitable coupling protein, resulting in the hydrolysis of polyphosphatidyl inositol to form diacylglycerol and inositol 1,4,5-triphosphate. Inositol 1,4,5-triphosphate stimulates the release
of calcium from intracellular stores (Strep et al., 1983). Protein kinase 'C' has been reported to phosphorylate NADPH oxidase, an enzyme of the plasma membrane which catalyses the reduction of oxygen to superoxide anion (Cox et al., 1985). The inhibition of the chrysotile stimulated generation of active oxygen species by the putative protein kinase 'C' inhibitors, sphingosine, fluphenazine, and staurosporine further suggested that chrysotile does not directly activate the NADPH-oxidase, but rather acts through protein kinase 'C' (Roney & Holian, 1989). However, further studies in this direction are needed to both pin point the role of asbestos mediated generation of reactive oxygen species and other cytotoxic mediators in asbestos-associated lung diseases, and its prevention by exploiting the scavenging characteristics of physiological and synthetic antioxidants and biomodulators.

Mesothelioma

Diffuse malignant mesothelioma is a fatal tumor arising from mesothelial cells or underlying mesenchymal cells in the pleura, pericardium, and peritoneum (Selikoff et al., 1980; Chretien et al., 1985; McDonald & McDonald, 1987a; Connelly et al., 1987). The time between diagnosis and initial occupational exposure to asbestos commonly exceeds 30 years (Wagner & Elmes, 1981). There are evidences that the risk of pleural mesothelioma increases with both intensity and duration of exposure (Newhouse et al., 1972; Whitwell et al., 1981), however, exposures in some cases have
been as short as 6 weeks (Newhouse et al., 1972). Mesothe-
liomas also have been observed after household exposure of
family members of asbestos workers and in individuals living
in close proximity to asbestos mines (Anderson et al.,
1976).

Although mesothelioma has been considered by some as a
disease pathognomonic of exposure to asbestos, approximately
20 to 30% of mesotheliomas occur in the general population
in adults not exposed occupationally to asbestos (Hirsh et
al., 1982). Mesotheliomas are rarely found in children.
Smoking evidently does not enhance risk of mesothelioma in
asbestos workers (Mossman & Gee, 1989). It has also been
reported that the proportional mortality is greatest in
workers exposed exclusively to amphiboles (10.6%) followed
by mixed exposures (3.6%) and exposure to chrysotile alone
(0.2%). (McDonald & McDonald, 1987b).

The cause effect association of asbestos and mesotheli-
oma has been amply confirmed by animal experimentation
(Wagner et al., 1973; Craighead et al., 1987). Several
studies have shown that mesotheliomas are induced in a
dosage-dependent fashion after intrapleural and intraperito-
neal injection of asbestos fibers into rodents (Pott &
Friedrichs, 1972; Wagner et al., 1974; Davis et al., 1986;
Jaurand et al., 1987). Moreover, extraction of polycyclic
aromatic hydrocarbons from fibers does not cause a decrease
in numbers of tumors in animals (Scheuer et al., 1973).
Trace metals were similarly not demonstrated to have any
effect on mesothelioma induction.

Exposure of rat and human mesothelial cells to asbestos consistently causes chromosomal aberrations such as polyplody, translocation, fragmentation, and sister chromatid exchanges (Sincock & Seabright, 1975; Oshimura et al., 1984; Lechner et al., 1985; Paterour et al., 1985; Jaurand et al., 1986; Achard et al., 1987; Wang et al., 1987; Jaurand, 1989; Nahid et al., 1991). However, unlike most carcinogens, asbestos fibers are not directly electrophilic, do not form adducts with DNA (Barrett et al., 1990). Asbestos has been reported to have weak mutagenic activity at the hypoxanthine guanine phosphoribosyl transferase (HGPRT) locus in the culture of Chinese hamster ovary cells (Rahman et al., 1983). The morphological transformation induced by chrysotile and crocidolite in Syrian hamster embryo cells is reported to be indistinguishable from cell transformation induced by other carcinogens such as benzo(a)pyrene (Hesterberg & Barrett, 1984). Many other cytogenetic analysis on a number of human mesotheliomas and derived cell lines have been also performed to elucidate a possible mesothelioma-specific chromosomal change and/or oncogene involved in tumor development (Gibas et al., 1986; Stenman et al., 1986; Popescu et al., 1988). However, results to date appear negative.

In view of the entrance and accumulation of asbestos fibers in various cell types and even in other sub-cellular organelles such as nucleus and phagosomes (Stoner et al., 1982; Johnson & Davies, 1983; McDonald & Kane, 1986), the interaction of silicic acid with calf thymus DNA in vitro
was studied in order to assess its role in the initiation of multistage process of carcinogenesis i.e. Mesothelioma (Gloag, 1981; Khan et al., 1988 & 1991a).

From the above discussion it appears that there are multiple mechanisms involved in the development of mesothelioma among occupationally asbestos exposed population. As discussed asbestos fibers do not induce gene mutations, but they are effective inducers of chromosomal alterations and DNA damage which may result in alteration of particular gene functions. Thus, with regards to the carcinogenic process there is as yet no consensus of scientific opinion about what actually happens at the cellular level to instigate the neoplastic reaction by asbestos fibers. The identification in human mesothelioma of activated transforming genes will be important in the future to understand the molecular basis of the asbestos-mediated cell transformation and carcinogenesis. This will further yield new insights into asbestos induced carcinogenicity.

Bronchogenic Carcinoma

Bronchogenic carcinoma is a kind of pulmonary tumor arising from the epithelial cells, lining the upper airways. Although the incidence of this tumor is increased in smokers in the general population (10-fold increase in comparison to non smokers), smoking individuals with occupational exposure to asbestos exhibit an even greater risk, i.e. 80-90 fold (Hammond, 1972; Selikoff et al., 1980; Mossman, 1988). The
potentiating effects of exposure to asbestos and cigarette smoke on the development of bronchogenic carcinoma have been documented extensively and verified by both epidemiological and experimental studies (Berry et al., 1972; Pylev & Shabad, 1973; Saracchi, 1977; Meurman et al., 1979; Topping & Nettleshiem, 1980; Mossman & Craighead, 1982; Mossman et al., 1983; Fisher & Gallo, 1988).

However, elucidation of the mechanisms of asbestos induced lung cancers in smokers has been the subject of much speculations. It has been known for several years that asbestos fibers adsorb polycyclic aromatic hydrocarbons present in cigarette smoke and increase cellular uptake and metabolism of these carcinogens (Lakowicz et al., 1978; Lakowicz & Bevan, 1979; Eastman et al., 1983) thereby producing the carcinogenic effects. In the induction of bronchogenic carcinoma, it is vital that the inhaled carcinogen be retained by the lung (Lakowicz & Bevan, 1979). Since, asbestos is known to efficiently retained in the lung (Pylev et al., 1969; Shabad et al., 1974), the adsorption of the carcinogen to the particulate may retard the pulmonary clearance of the carcinogen, thus enhancing the total exposure level to the carcinogen and prolonging the duration of contact with the site of metabolic activation to ultimate carcinogens. This hypothesis was not accepted later as some of the non carcinogenic particulate materials also transport these carcinogens (Harvey et al., 1984).

According to a recent hypothesis, fibers adsorb phospholipids on their surfaces either from surfactants or from
cell membranes. This then creates an avenue for lipophilic chemical carcinogens of tobacco smoke e.g. PAHs to diffuse within all lipid environment across the aqueous regions of the bronchial lining layer into the cellular membrane of the bronchial epithelium (Gerde & Scholander, 1987). This suggested lipid linked mechanism can give rise to very local but extremely high cellular doses of carcinogens at the preferential sites of asbestos and smoke deposition in the lung. Consequently, this may contribute to strong synergism observed between smoking and asbestos exposure for the induction of lung cancer in asbestos workers. In addition, other interactions between asbestos and components of cigarette smoke may contribute to their multiplicative effects in the development of lung tumors. For example, smoking inhibits the clearance of asbestos and increases the proportion of fibers penetrating airway walls (McFadden et al., 1986a & b). Moreover, cigarette smoke also reduced the levels of antioxidants, depress proteinase inhibitors, generate free radicals and stimulate cell transformation (Nakayama et al, 1984; Pryor et al., 1984; Keith & Mossalder, 1986). Furthermore, it is very well documented in the literature that PAHs are not carcinogenic by themselves but on metabolic activation, they are converted into the ultimate carcinogens (Gelboin, 1980). Based on these facts, one of the possible mechanisms by which asbestos can enhance the development of lung cancer in smokers, exposed to asbestos may be related to their effects on drug metabolizing
enzymes. There are reports that asbestos alters the activity of drug metabolizing enzyme system (Rahman et al., 1990; Khan et al., 1991b). It is reported that chronic smoke exposure increases the activity of pulmonary aryl hydrocarbon hydroxylase (AHH) in mice and thereby affect the metabolism of benzo(a)pyrene (Abramson & Hutton, 1975). This induction of AHH affect the synergism between smoke and asbestos in the high risk of bronchogenic carcinoma formation in asbestos workers with smoking habits.

Until quite recently, it was unclear how asbestos triggered proliferation on tracheal epithelial cells. However, several studies suggest that mechanisms of cell signalling by asbestos are similar to those observed with TPA, a soluble tumor promoter that binds directly to protein kinase 'C' (PKC), a calcium and phospholipid-dependent enzyme that activates a limb of the phosphoinositides signal transduction pathway (Nishizuka, 1986). Mitogenic concentrations of crocidolite asbestos caused increased accumulation of diacylglycerol in tracheal epithelial cells (Sesko et al., 1990) and subsequent activation of PKC (Pederiset et al., 1991), presumably by activation of membrane phospholipases. The increased production of inositol tris- and tetrakisphosphates appeared responsible for the generation of diacylglycerol, which preceded increased cell division. Abrogation of crocidolite-induced ornithine decarboxylase (ODC) activity in tracheal epithelial cells by inhibitors of PKC and calcium channel antagonists (Marsh & Mossman, 1988) suggest that PKC is related causally to asbestos associated
cell proliferation. Furthermore, the early rapid induction of ODC activity after exposure of tracheal epithelial cells to either asbestos or oxidants occurs at the level of transcription as suggested by a corresponding proportional increase in the expression of the total mRNA for ODC (Marsh & Mossman, 1991). They also suggested that $\text{H}_2\text{O}_2$ plays a major role in asbestos stimulated ODC induction and proliferation of epithelial cells of the respiratory tract by altering the regulation of a gene critical to proliferation.

At this stage it may be suggested that asbestos fibers might facilitate the initiation of lung cancer in smokers by virtue of their size and physico-chemical state, adsorption and transport of the carcinogenic constituents of cigarette smoke such as PAHs, increase in both retention and binding of lipophilic carcinogens with DNA in tracheal epithelial cells, oxygen free radical production, alterations in the activities of related enzymes and release of mediators of cytotoxicity that collectively play a role in tumor promotion. Furthermore, the persistence of the fibers may allow multiple hits with time, resulting in neoplastic progression.

Other Problems Associated with Asbestos Exposure

A number of benign pleural changes that rarely cause functional impairment have been observed in asbestos-exposed workers. These include pleural effusions, pleural fibrosis, pleural plaques, that is, accumulations of a cellular colla-
gen on the diaphragm and chest wall, and pseudotumors or infoldings of the lung often associated with plaques. (Hillerdal, 1981; Hillerdal & Ozesmi, 1987; Martensson et al., 1987). These pleural changes may reflect exposure to asbestos but have no demonstrated relation to the development of mesothelioma.

Some other parts of the body are occasionally affected by asbestos. For example, tumors of the gastrointestinal tract, larynx and other organs including the kidney, ovary, pancreas, pericardium, eye and lymphatic system, have been reported in some cohorts of asbestos workers (Doll & Peto, 1987; Hart, 1987; Kogan et al., 1987; Chan & Gee, 1988; Edelman, 1988). Both laryngeal and gastrointestinal tumors have other etiologies such as smoking, alcohol, diet and intestinal polyposis that confound the interpretation of epidemiologic data.

3. KEROSENE

Kerosene is one of the several petroleum distillates prepared by the fractionation of crude petroleum oil with carbon chain lengths that range from C9 to C16 carbon atoms per molecule and distills between 175 and 325°C (API Toxicological review, 1967).

Kerosene is used as a fuel, as a carrier for pesticides, as a weed killer, as a mold release agent in the ceramic and pottery industry, as a cleaning solvent, and in asphalt coatings, enamels, paints, thinners and varnishes.
Physico-chemical Properties

Physically, kerosene is usually a pale yellow or water-white, mobile, low volatile, oily liquid that has a flash-point (closed cup) of about 38-74°C and is therefore considered a combustible compound. The composition of kerosene varies depending on the source of crude oil and the method of refining. Kerosene is a complex mixture of aliphatic, naphthenic, and alkylated aromatic hydrocarbons. A typical analysis of kerosene indicates that there are about 25% normal paraffins, 12% branched paraffins, 30% monocycloparaffins, 12% dicycloparaffins, 1% tricycloparaffins, 16% mononuclear aromatics, and 5% dinuclear aromatics (Rossini et al., 1953). The aromatic content of kerosene ranges from 5 to 20% (API Toxicological reviews, 1967). The predominant aromatic molecular types include diphenyls, methylnaphthalenes, and tetralins (API Toxicological reviews, 1967). However, emissions from unvented kerosene heaters i.e. soot, contains polycyclic aromatic hydrocarbons (PAHs), nitrated PAHs, alkylbenzenes, pentachlorophenol, phthalates, hydro-naphthalenes, aliphatic hydrocarbons, alcohols, ketones and other organic compounds (Olson & Calcote, 1980; Gharaibeh et al., 1988). Additional chemical and physical properties of kerosene are given in Table 3.

Toxicity

Due to extensive use of kerosene in various lifestyle practices, it creates numerous health-associated problems
Table 3.
Physical and chemical properties of kerosene.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling range</td>
<td>175-325°C</td>
</tr>
<tr>
<td>Predominant molecular species</td>
<td>C9-C16</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>Approximately 170</td>
</tr>
<tr>
<td>Appearance and odour</td>
<td>Water-white to straw</td>
</tr>
<tr>
<td></td>
<td>coloured, odourless-aromatic</td>
</tr>
<tr>
<td>Specific gravity (20/4°C)</td>
<td>0.8</td>
</tr>
<tr>
<td>Vapour pressure (mmHg)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Vapour density (air=1)</td>
<td>4.5</td>
</tr>
<tr>
<td>Solubility</td>
<td>Insoluble in water</td>
</tr>
<tr>
<td>Evaporation rate</td>
<td>Unknown</td>
</tr>
<tr>
<td>Autoignition point</td>
<td>229°C</td>
</tr>
<tr>
<td>Flashpoint range (closed)</td>
<td>37.8-73.9°C</td>
</tr>
<tr>
<td>Flammable limits (in air)</td>
<td>0.7-5.0%</td>
</tr>
<tr>
<td>Flammability category</td>
<td>Class IB</td>
</tr>
<tr>
<td>Extinguishing media</td>
<td>Foam, carbon dioxide,</td>
</tr>
<tr>
<td></td>
<td>dry chemicals</td>
</tr>
</tbody>
</table>
which have been studied by many researchers and verified by both epidemiological and experimental studies.

(i) Epidemiological Studies

There are numerous cases of kerosene poisoning by aspiration or ingestion of the liquid (Hiebel et al., 1963; Truffa & Montalenti, 1969; Mahdi, 1988). Hiebel et al., (1963) found three cases of bone marrow suppression associated with dermal and oral exposure to kerosene. Study of the bone marrow suggested that it was hypocellular with normoblastic erythropoiesis, "toxic" granulopoiesis, increased eosinophils and decreased neutrophils. They also postulated a mechanism for bone marrow suppression on the basis of the fact that kerosene penetrates the heavy fat content of the marrow.

Furthermore, Mahdi (1988) reported a prospective study of 70 children aged between 9 months and 6 year who were admitted to the Children's Hospital in Riyadh having ingested kerosene. The majority came from the low socioeconomic class where illiteracy, poor housing and overcrowding was predominant. Lack of supervision and availability of kerosene in utensils ordinarily used for drinking was the major predisposing factor. Twenty three patients (33%) were asymptomatic. Cough, vomiting, dyspnoea, and fever were the most common symptoms observed. Radiological signs of pneumonia were shown in nine out of 27 patients who had chest X-rays. There was one death.
In 1955, Johnson reported the case of a 58 year old man exposed to a degreasing solvent containing kerosene. She found that the patient illness was diagnosed as typical hypoplastic anemia with pancytopenia and hypoplastic marrow with no evidence of leukemia. Further, she suggested that benzene or other aromatic compounds were components of kerosene and might have been responsible for the blood effects, but she did not have quantitative data on the benzene content.

Grant (1974) has commented that kerosene and deodorized kerosene were essentially innocuous to the human cornea but no details were given. There is no present reason for suggesting that the solvents, if they are free of carcinogenic aromatics such as benzene, would cause cancer, birth defects, or germinal mutations. However, Downing (1952) related that a man exposed to various solvents and greases including kerosene developed a epidermoid carcinoma. The etiologic agent responsible for the carcinoma was unknown since the worker was exposed to a wide variety of substances.

(ii) **Experimental Studies**

Light petroleum hydrocarbons, such as kerosene, have a low toxicity when ingested and retained in the stomach, but if the solvent is aspirated directly into the lungs, extensive lung damage and death can occur (Gerarde, 1963; Steele et al., 1972).
The characteristic lesions resulting from the aspiration of liquid hydrocarbons into the tracheobronchial tree is an acute, fulminating, hemorrhagic and often fatal bronchopneumonia, it may appear within minutes or be delayed for several hours (Soule & Foley, 1957). The progress of the pulmonary disease may be followed roentgenographically by observing the extent to which the lung field becomes opacified (Reynolds & Bonte, 1960). Early and widespread pulmonary changes may be found even in the absence of clinical signs (Brunner et al., 1964), and conversely pulmonary symptoms may precede lung X-ray changes (Vaziri et al., 1980). Death may result from asphyxia secondary to intense pulmonary edema and consolidations (Scott, 1944).

Hydrocarbon aspiration is responsible for substantial morbidity in both children and domestic animals (Burgeson et al., 1975; Zucker et al., 1986). However, Goodwin et al. (1988) have reported that aspiration of kerosene to mongrel dogs resulted in severe pulmonary dysfunction with acute, severe and persistent intrapulmonary physiologic shunting, hypoxemia, bradycardia and hypotension. Although, some evidences may indicate gastrointestinal absorption of hydrocarbons, the primary insult is from intratracheal aspiration (Richardson & Pratt-Thomas, 1951; Soule & Foley, 1957; Dice et al., 1982). The physiologic findings of Goodwin et al. (1988) are consistent with previous data that have shown tachypnea and arterial hypoxemia at 24 hour after kerosene aspiration (Steele et al., 1972) and with those that showed decreases in lung compliance, total lung capacity, and
thoracic gas volume of dogs 1 hr. after 0.3 ml kerosene/kg was instilled intratracheally (Scharf & Prinsloo, 1982). One study reported an alteration in the surface tension properties of pulmonary surfactants extracted from the lungs of animals that had aspirated furniture polish, a hydrocarbon-containing substance (Giammona, 1967). This suggests alveolar instability, which would increase intrapulmonary physiologic shunting. Further, the pathologic effects of kerosene aspiration described by others (Ashkenazi & Berman, 1961; Giammona, 1967; Scharf & Prinsloo, 1982) namely hemorrhagic necrosis, intra-alveolar edema, epithelial destruction and inflammatory exudation, all would be expected to have the physiologic effect that occurred in the animals.

Intratracheal administration of kerosene to rats at a dose of 0.2 ml developed noisy and labored ventilation, and frequent frothy nasal discharge of serosanguinous appearance (Schwartz et al., 1965). The gross adverse effect was that of a hyperemic and hemorrhagic pulmonary parenchyma. Microscopic examination of the tissue showed marked diffuse capillary engorgement, venous congestion, intraalveolar edema and a frequent occurrence of subepithelial vacuolation with separation of the bronchial lining (Schwartz et al., 1965). Furthermore, kerosene at sublethal doses of 0.05 ml and 0.02 ml injected intratracheally produced either an acute exudative reaction or a chronic proliferative inflammation (Gross et al., 1963). They reported that the acute
reaction was mainly of a leukocytic character and involved scattered, small clusters of alveoli. Other alveoli contained exudates consisting mainly of serous fluid or fibrin. In general, the acute inflammatory response was of mesodermal origin. On the other hand, the chronic inflammation was characterized by the enlargement of visible alveolar cells and an increase in their number. Many of the cells had large excessively dark, round nuclei, and basophilic, lacy cytoplasm. The vascular periaventitial tissue was usually edematous and infiltrated by sparsely distributed monocytes. In general, the chronic inflammation was of endodermal origin.

Kerosene and related hydrocarbons are also irritating to skin and mucous membranes and percutaneous absorption is sometimes significant. On prolonged and extensive contact, kerosene and its congeners can produce epidermal necrolysis (Barnes & Wilkinson, 1973).

Lupulescu et al. (1973a) concluded that exposure of the skin to liquid kerosene caused large lacunae in the horny spinous cells and marked nuclear changes. Both the stratum corneum and stratum spinosum were affected by kerosene. While intracellular edema and disruption of the tonofilaments occurred in many types of epidermal damage, Lupulescu and associates considered the observed changes in the keratin pattern to be specific effects of liquid kerosene exposure. In another report, Lupulescu et al (1973b) described the penetration and transport of kerosene by exposing the human skin to tritiated kerosene for 90
minutes. Electron microscopic autoradiographic studies showed that most of the kerosene was present over the horny layers, in the intracellular spaces of the stratum spinosum, and between desmosomes. Kerosene was also found surrounding the nuclear chromatin of spinous cells. They have also suggested that the presence of labelled kerosene in the nucleus may have interfered with mitosis.

The chief systemic reaction to kerosene is central nervous system depression (Jaeger et al., 1978). Hydrocarbons of all types induce central nervous system depression, but the aliphatic hydrocarbons which predominate in petroleum distillates are said to produce profound coma with an inhibition of deep tendon reflexes, whereas the coma from aromatic hydrocarbons was characterized by motor restlessness, tremors and hyperactive reflexes (Von Oettingen, 1940). However, Jaeger et al (1978) have suggested that central nervous system depression by kerosene is due to anoxia caused by pulmonary edema and hemorrhagic as well as pneumonitis and in aromatic hydrocarbon intoxication, the central nervous system stimulation appears associated with coma and cardiac arrhythmias.

Inspite of various pathophysiological effects of kerosene, a little is known about the biochemical effects caused by kerosene exposure. Biochemical and hematological studies in male wistar rats after repeated subcutaneous administration of kerosene showed treatment related increases in the weights of liver, spleen, and peripheral lymph nodes at
necropsy (Rao et al., 1984). Correspondingly they have also reported increases in DNA, RNA, protein and lipid contents of liver and spleen, an increase in alkaline phosphatase and a decrease in benzo(a)pyrene hydroxylase levels in liver. Furthermore, they found a significant diminution in serum cholinesterase, carboxylesterase, and albumin levels, while serum alkaline phosphatase levels were found to be greatly enhanced. In an early study on rats, Rao and Pandya (1980) have observed inhibitory effects of kerosene and gasoline in liver heme biosynthesis as evidenced by the decreased enzymatic activities of \(\delta\)-aminolevulinic acid synthetase and \(\delta\)-aminolevulinic acid dehydratase. Further, Starek et al (1975) have reported an increase in the activities of serum aspartate aminotransferase, alanine aminotransferase and malate dehydrogenase.

The biochemical mechanisms involved in the bronchoconstriction and airway hyperresponsiveness induced by the acute inhalation of aerosol of kerosene in experimental animals and the inflammatory changes induced by subchronic inhalation of the aerosol of kerosene smoke have been approached recently by Mesa et al (1988). They suggested that the inhibition of acetylcholinesterase activity in airway and the decrease in the efficiency of calcium uptake by the sarcoplasmic reticulum are some of the mechanisms involved in the airway hyperreactivity induced by kerosene. However, Casaco et al. (1985) previously reported the tracheal acetylcholinesterase inhibition induced by kerosene that could actually increase the acetylcholine concentration in
the smooth muscle of airways. The subchronic exposure to vapours of kerosene or its combustion fumes, induced an increase in the activity of lysosomal enzymes in lungs which can be an explanation of the inflammatory response induced in lungs (Mesa et al, 1988).

The histopathological alterations of the respiratory tract and other organs exposed to kerosene were reported by several investigators (Rao et al, 1984; Sanabaria et al, 1984; Noa & Illnait, 1987; Upreti et al., 1989). Histologic examination of trachea and lungs after kerosene exposure showed the erosion of tracheal epithelium and inflammatory infiltration, and thickening of interalveolar septa (Sanabaria et al., 1984). They also reported that the eosinophilic infiltration may represent an immunological response resembling reactions of immediate hypersensitivity. Moreover, Noa and Illnait (1987) have found that kerosene exposure engendered aortic plaques with fibrous tissue, collagen, and elastic fibers embedded in abundant glycosaminoglycans-rich ground substance interspersed in which are smooth muscle cells resembling those seen in atherosclerosis, and changes in levels of blood lipid. However, Rao et al., (1984) revealed treatment related lesions in many organs, e.g. liver, spleen, thymus, kidney, adrenal and lymph nodes. They observed enlargement, necrosis and cavitation of liver with chronic venous congestion and subsequent diffuse fibrosis. Kidney presented conspicuous lesions in the cortical region. The presence of aggregates of mononuclear inflamma-
tory cells in the vicinity of glomeruli might be attributed to the likely involvement of some immune mechanisms in kidney. Spleen was found markedly enlarged with an increased lymphopoiesis and lymphoblastogenesis in the lymph nodes. However, thymus presented no marked alterations in the weight and its cellular constituents, though histological alterations such as mild atrophy of thymic lobules with depletion of lymphocytes in cortex were noticed. They have summarized the observations in lymphoid organs after kerosene exposure that these may interfere in immune functioning (Rao et al., 1984).

Furthermore, some reports on the mutagenic activity of kerosene soot are also existed (Skopek et al., 1979; Yamana-ka & Maruoka, 1984; Mumford et al., 1992). They have reported an increase in mutagenic activity with Ames' *Salmonella typhimurium* assay system and the increased mutagenic activity may be attributed to substances derived from the kerosene heater and the inhabitants, living activity other than smoking.

4. Concluding Remarks

The survey of the literature on asbestos indicated that its physical, chemical, biochemical, clinical and pathophysiological aspects have been extensively studied and upto some extent the same studies have also been done with kerosene and its soot. Epidemiological surveys and experimental studies also revealed that cigarette smoke augments the pathological responses of asbestos. There are possibilities
of exposure of asbestos workers to many other compounds at worksite and also at home which can increase the toxic responses. Among them the exposure to kerosene is quite common in India. The author of the present dissertation became interested to take up suitable chemical, biochemical and histopathological parameters to study the effects of kerosene-mediated toxic manifestations in asbestos-exposed lungs, with special reference to cytotoxic, fibrogenic and carcinogenic potential.