Asbestos: Scientific Developments and Implications for Public Policy

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Asbestos is a commercial term for a group of fibrous minerals often associated with the development of pulmonary interstitial fibrosis (asbestosis), lung cancer, and malignant mesothelioma in occupationally exposed individuals. The pathogenicity of different forms of asbestos varies—long, thin amphibole fibers are most pathogenic, particularly in the induction of mesothelioma. Available data do not support the concept that low-level exposure to asbestos is a health hazard in buildings and schools. The concentration of asbestos fibers in air, type of asbestos, and size of fibers must be considered in evaluation of potential health risks.

ASBESTOS ENGENDERS BOTH FEAR AND PANIC IN U.S. society. Observation that asbestos-containing materials (ACM) have been used in schools, buildings, and hospitals, and the Asbestos Hazard Emergency Response Act (AHERA), a mandate from the Environmental Protection Agency (EPA) that requires inspection of the nation's public and private schools for asbestos, have resulted in the explosive growth of asbestos identification and removal companies. By EPA estimates, extension of EPA requirements to approximately 733,000 public and commercial buildings containing asbestos will cost $53 billion, discounted at 10% over 30 years (*1*). Because of uncertainties regarding the amount of asbestos and its condition in these buildings, estimates for removal of asbestos are as high as $100 to $150 billion (*2*).

Asbestos was shown to cause asbestosis at the turn of the century. Its association with the causation of lung and pleural tumors in asbestos miners and workers was demonstrated in the 1950s and 1960s, respectively (*3*). An important issue is whether these diseases are also hazards to the general population exposed to airborne levels of asbestos in schools and other buildings. Does available evidence support the concept that asbestos causes disease in the nonoccupational environment? What are the mechanisms of asbestos-induced fibrogenesis and carcinogenesis? Most importantly, have recent data been adequately considered in formulating policies in the United States for regulation and banning of asbestos? In this article, we summarize recent developments and discuss their implications for public policy.

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Physico-Chemical Characteristics of Asbestos

"Asbestos" is a broad commercial term for a group of naturally occurring hydrated silicates that crystallize in a fibrous habit. The legal definition of a fiber as promulgated by the EPA and other U.S. regulatory agencies is one that possesses a $\geq 3:1$ aspect ratio. However, this definition has been criticized by mineralogists (*4*).

Asbestos fibers in ores are not respirable until released and made airborne during mining and processing. The family of asbestos minerals can be subdivided into serpentine and amphibole fibers (Fig. 1). Chrysotile, which accounts for over 90% of the world's production of asbestos, is the most common fibrous serpentine, whereas the amphiboles, a chemically diverse group of less industrially important minerals, include the fibrous minerals and crocidolite, amosite, anthophyllite asbestos, actinolite asbestos, and tremolite asbestos. Tremolite, actinolite and anthophyllite, which occur in both fibrous and nonfibrous forms, have been only rarely mined for use as commercial asbestos. Both the fibrous and nonfibrous forms of these amphibole minerals are sometimes found as contaminants of commercial deposits of chrysotile, talc, vermiculite, and other minerals (*4*). The nonfibrous forms of crocidolite and amosite are referred to as riebeckite and grunerite, respectively.

The various types of asbestos fibers differ in their chemical composition, morphology, and durability. Therefore, the biologic effects should be considered individually for each fiber type. Identification of specific types of asbestos in air samples requires sophisticated technology such as transmission electron microscopy, x-ray diffraction, or energy dispersive x-ray spectroscopy. The rod-like amphiboles appear to penetrate the peripheral lung more readily

Table 1. Summary statistics for average airborne fiber concentrations in U.S. schools (*88*) and buildings (*89*). The data used in the calculation of each statistic are the average concentrations (expressed as number of fibers greater than 5 μm in length per cubic centimeter of air) in a building (for indoor samples) or the concentration outside each building [for outdoor samples (*89*)]. By visual inspection, category 1 buildings contained no asbestos-containing material (ACM), category 2 buildings contained ACM in primarily good condition, and buildings in category 3 showed at least one area of significantly damaged ACM. In the study on public buildings, 387 indoor and 48 outdoor air samples were evaluated. No asbestos fibers were detected in 83% of the 387 samples. The sample size is given in parentheses below each heading.

Statistic	Schools (71)	Outdoor air (48)	Public buildings		
			Category 1 (6)	Category 2 (6)	Category 3 (37)
Median		0.00000	0.00010	0.00040	0.00058
Mean	0.00024*	0.00039	0.00099	0.00059	0.00073
SD	0.00053	0.00096	0.00198	0.00052	0.00072

*80th percentile = 0.00045; 90th percentile = 0.00083.

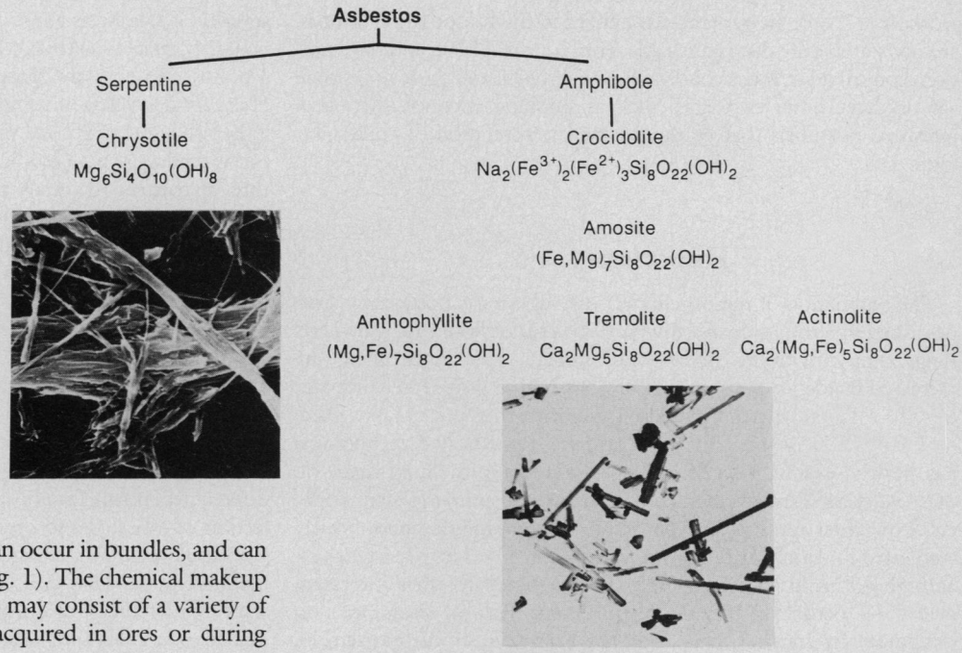

Fig. 1. Classification and morphology of asbestos fibers. The inserted photographs are scanning electron micrographs of Union Internationale contre le Cancer reference samples of chrysotile A (**left**) and crocidolite asbestos (**right**) (field of view is ~12 μm in both photographs). The amphiboles are depicted in order of their relative industrial importance.

than chrysotile fibers, which are curly, can occur in bundles, and can be intercepted at airway bifurcations (Fig. 1). The chemical makeup of each fiber type is complex, and fibers may consist of a variety of trace metals and organic compounds acquired in ores or during processing.

Asbestos is attractive to industry because of its resistance to heat and chemicals, high tensile strength, and lower cost compared to man-made materials. Although use of spray-on asbestos as a fireproofing material or insulation has been banned in this country, as well as in several European countries, asbestos is incorporated currently into cement construction materials (roofing, shingles, and cement pipes), friction materials (brake linings and clutch pads), jointing and gaskets, asphalt coats and sealants, and other similar products. As a result of these applications, an estimated 20% of buildings including hospitals, schools, and other public and private structures contain ACM (*1*). Asbestos in buildings does not spontaneously shed fibers, but physical damage to ACM by decay, renovation, or demolition can cause release of airborne fibers (*5*).

Diseases Associated with Occupational Exposure to Asbestos

Occupational exposure to asbestos can cause four types of disorders: asbestosis; lung cancer; mesotheliomas of the pleura, pericardium, and peritoneum; and benign changes in the pleura (*3*). Asbestosis, a pulmonary interstitial fibrosis with excessive deposition of collagen, caused progressive lung stiffening, impaired gas exchange, disability, and death in many workers exposed before the enforcement of occupational standards. Lung cancers, that is, tumors arising in tracheobronchial epithelial or alveolar epithelial cells, have occurred in asbestos workers in most cases 20 or more years after their first exposure to asbestos. In general, lung cancers have been found in asbestos workers who are smokers and only rarely in nonsmokers (*6*). A number of epidemiologic studies have indicated that the relation between the development of lung cancers and cumulative exposure to asbestos is approximately linear, but wide variations in slope of the line occur apparently related to fiber type and industrial usage (*7*). Death rates from lung cancers in asbestos workers, as measured by standard mortality ratios (SMRs), the observed mortality of a cohort divided by the mortality of a control population, are lowest in chrysotile miners and workers manufacturing friction materials. In contrast, lung cancer deaths are higher in those mining and working with amphibole asbestos. Textile workers in a South Carolina plant in which chrysotile was used exhibited a striking increase in lung cancers with duration of exposure when compared to Canadian chrysotile miners and millers. Solvents and oils in textile production might act as cocarcinogens in the development of these lung tumors (*7*).

Diffuse malignant mesothelioma is a fatal tumor arising from mesothelial cells or underlying mesenchymal cells in the pleura, pericardium, and peritoneum (*8*). The time between diagnosis and initial occupational exposure to asbestos commonly exceeds 30 years. Smoking evidently does not enhance risk of mesothelioma in asbestos workers (*3*). Although mesotheliomas are extremely rare malignancies, that is, only 1648 were recorded from 1973 to 1984 in one survey covering approximately 10% of the U.S. population (*9*), they may account for as much as 18% of the proportional mortality in crocidolite workers (*10*). Mesotheliomas also have been observed after household exposure of family members of asbestos workers and in individuals living in close proximity to asbestos mines (*11*). 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 (*12*). Mesotheliomas are rarely found in children.

Diagnosis of mesotheliomas is a challenge as the tumor may resemble metastases of other tumor types occurring in the pleura or peritoneum and assume a wide variety of microscopic appearances. Thus, death certificates may either underestimate (because these tumors are attributed to cancers of the gastrointestinal tract and other organs) (*13*) or overestimate the incidence of mesotheliomas. In France, mesotheliomas are overestimated by a factor of 3 on death certificates in comparison to the mesothelioma registry (*14*).

A number of benign pleural changes that rarely cause functional impairment have been observed in asbestos workers. These include pleural effusions, pleural fibrosis, pleural plaques, that is, accumulations of acellular collagen on the diaphragm and chest wall, and pseudotumors or infoldings of the lung often associated with plaques. These pleural changes may reflect exposure to asbestos but have no demonstrated relation to the development of mesothelioma.

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 (*13, 15*). In general, the enhanced SMRs for these tumors are not statistically distinguishable from normal SMRs and have not been confirmed in most cohorts. Both laryngeal and gastrointestinal tumors have other etiologies such as smoking, alcohol, diet, and intestinal polyposis that confound the interpretation of epidemiologic data.

The Amphibole Hypothesis

The association of mesothelioma with asbestos exposure was first described in 1960 in the northwest Cape area of South Africa where long, thin crocidolite fibers were mined (*16*). Since then, an increased incidence of mesothelioma has been reported in a number of occupational settings including factories that presumably used only chrysotile. Within the past decade, sophisticated technology has allowed examination of the types of fibers in the lung tissue of these workers. Results revealed that many chrysotile-exposed workers showed an appreciable lung burden of amphibole fibers, which were used for brief periods in the workplace (*17*). The persistence of amphiboles in human lungs may be attributed to their increased ability to penetrate the peripheral lung, lack of clearance, or durability. In contrast, chrysotile has been found post-mortem in smaller amounts than expected in the lungs of asbestos workers (*18*). It disappears with time most likely because magnesium and silica are leached from the fibers (*19*). Recently, the lung content of asbestos and nonasbestos fibers has been compared in diagnosed cases of mesothelioma, lung cancer, and cardiovascular disease (controls) from the western coast of France, a region containing shipyards (*20*). The number of amphibole fibers (crocidolite and amosite) was significantly higher in lungs from mesothelioma patients, whereas numbers of chrysotile and nonasbestos fibers were similar in all groups. These data suggest that the lung burden of chrysotile and nonasbestos fibers bears no relation to the occurrence of these cancers.

Several recent studies indicate that the risk of pleural mesothelioma is lower where chrysotile is used without admixture or contamination by amphiboles (*21*). For example, a gradation of death rates from mesothelioma has been observed in both male and female asbestos-exposed cohorts. Mesothelioma has been responsible for approximately 6 to 8% of the proportional mortality in men working with mixtures containing crocidolite or amphibole (crocidolite or amosite) in comparison to less than 1% of the proportional mortality in men working with chrysotile (*10*). In female cohorts, the proportional mortality from mesothelioma was highest for amphibole exposure (10.6%) and lowest for chrysotile exposure (0.2%). Thus, these data suggest that amphiboles are the major cause of mesotheliomas in asbestos workers.

Chrysotile miners and millers in Quebec who were supposedly exposed only to chrysotile have developed few mesotheliomas (*22*). However, recent fiber analyses on the lungs of both these workers and chrysotile factory workers showed the presence of tremolite (*23*). This amphibole in the fibrous form has been implicated as the causative agent of mesotheliomas and lung cancers in miners exposed to vermiculite heavily contaminated with tremolite (*24*). Although tremolite composes less than 1% of the asbestos dust in the Quebec mines and mills, the relative ratio of tremolite to chrysotile fibers in the lungs of Canadian miners and millers is related directly to their risk of developing mesothelioma (*25*).

For the reasons above, the few mesotheliomas observed in Canadian chrysotile workers appear to be attributable to fibrous tremolite, an observation compatible with other evidence that amphiboles are the most pathogenic asbestiform minerals. Likewise, recent data on London asbestos factory workers show that the severity of asbestosis and carcinoma of the lung (as well as mesothelioma) correlates with the lung burden of crocidolite and amosite asbestos and that the proportions of chrysotile and nonasbestos fibers are decreased in comparison to matched control patients (*26*). A British cohort exposed since 1970 to chrysotile at airborne levels not exceeding 0.5 to 1.0 fiber per cubic centimeter in the manufacture of friction materials showed no excess of deaths from lung cancer, other asbestos-related tumors, or chronic respiratory disease (*27*). These and other data (*7, 17, 21, 28*) suggest that amphiboles are more potent than chrysotile in the induction of fibrotic lung disease and associated lung cancers.

Experimental Models of Asbestos-Induced Lung Disease

Several studies have shown that mesotheliomas are induced in a dosage-dependent fashion after intrapleural and intraperitoneal injection of asbestos and other asbestos-like fibers into rodents (*29*). Chrysotile was as carcinogenic as the amphiboles by these routes of administration. However, differences have been observed between the carcinogenicity of fibrous and nonfibrous materials. For example, in one study, fibrous tremolite was carcinogenic after intrapleural injection, whereas nonfibrous tremolite was noncarcinogenic at identical concentrations (*30*). Although the natural route of exposure to fibers by inhalation was circumvented in these experiments, they were useful in indicating that fibers longer than 8 μm and less than 0.25 μm in diameter have the most marked carcinogenic potential, that is, the "Stanton hypothesis." These data have been supported by the results of inhalation studies in rats in which short (≤5 μm in length) and long fiber preparations of amosite and chrysotile asbestos have been compared (*31*). In contrast to the batches of amosite and chrysotile asbestos containing many long fibers, short fibers of amosite produced neither asbestosis nor pulmonary tumors. Short chrysotile produced a small amount of asbestosis and malignancies, but these were attributed to contamination of the short chrysotile preparation by longer fibers. Fewer long than short fibers of both types were present in the lungs of all rats at the termination of exposure, but, regardless of size, fewer chrysotile fibers remained in the lung. These results support the observations that chrysotile fibers, in comparison to amphibole fibers, are cleared more rapidly from human lungs (*17*). This phenomenon and limited alveolar penetration of curly chrysotile bundles (rather than their inherent absence of carcinogenicity) may account for the apparent lack of association of chrysotile fibers with the development of mesothelioma in human cohorts.

The exorbitant costs of inhalation experiments with animals preclude long-term studies to determine the carcinogenic potential of asbestos at low-level exposures. The development of malignancies in rodents approaches the 2- to 3-year life-span of these animals (*32*), a period of too brief to reflect the consequences of the long-term solubility of chrysotile in the human lung.

Mechanisms of Asbestos-Induced Inflammation and Fibrogenesis

Both epidemiologic and experimental data support the concept of a threshold for chrysotile-induced pulmonary fibrosis. In a sheep model of asbestosis, inflammation and histopathologic evidence of disease were not observed after less than 100 mg of chrysotile were injected into the trachea of the sheep (*33*). After brief, intense inhalation of chrysotile, the sheep accumulated alveolar macrophages (AMs) at areas of deposition of fibers (*4*). These cell types are

viewed as "effector" cells of disease as they produce a mixture of fibroblast growth factors, chemotactic factors, and fibronectin. Prostaglandins, plasminogen activator, a heat-stable factor similar to platelet-derived growth factor (PDGF), lysosomal enzymes, and active oxygen metabolites, one or more of which may cause proliferation or functional impairment of neighboring epithelial cells and fibroblasts in the lung, were released after exposure of AMs to asbestos in vitro (*35*). These substances might mediate both acute and chronic inflammatory reactions in man and animals after inhalation of asbestos. In support of this hypothesis, AM-derived growth factor (AMDGF), PDGF, superoxide (O_2^-), and H_2O_2 were spontaneously released from AMs recovered by bronchoalveolar lavage from patients with asbestosis (*36*). Similarly, AMs lavaged from both mice and sheep that had an earlier intratracheal injection of chrysotile released enhanced amounts of a growth factor that stimulated proliferation of a human embryonic lung cell line (WI-38) (*37*).

In one study, AMs from both normal individuals and patients with idiopathic pulmonary fibrosis expressed a 4.2-kilobase messenger RNA complementary to c-*sis*, a proto-oncogene coding for the B chain of PDGF (*38*). The amounts were approximately fourfold higher from AMs of patients with pulmonary fibrosis. Because PDGF is mitogenic to mesenchymal cells, which possess functional PDGF receptors, elevated levels of PDGF in lung tissue or fluids could induce lung fibroblasts to divide or to produce exorbitant amounts of collagen, the hallmark of the fibrotic lesion. Quiescent human mesothelial cells also undergo DNA synthesis after exposure to PDGF and a broad spectrum of other growth factors (*39*).

Within the past few years, several laboratories have focused on active oxygen species (AOS) as causative agents of both asbestosis and asbestos-related malignancies. Increased amounts of superoxide (O_2^-) have been produced after rodent AMs were exposed in vitro to long asbestos fibers, whereas generation was minimal after shorter fibers and nonfibrous particles were introduced (*40*). Smaller fibers and particles are incorporated into phagolysosomes by AMs, whereas longer fibers are incompletely phagocytosed, a process liberating more AOS.

The observation that exogenous administration of scavengers of AOS prevents asbestos-induced cell death to cultures of tracheal epithelial cells and lung fibroblasts (*41*) suggests that AOS are intimately related to asbestos toxicity even in the absence of AMs. Fibers may induce generation of AOS after phagocytosis or by extracellular mechanisms. For example, recent studies with asbestos in cell-free systems have demonstrated by electron spin resonance that chrysotile, crocidolite, and amosite generate AOS in the presence of H_2O_2 or physiological saline (*42*). Under these circumstances, Fe^{2+} on the surface of the fiber appears to drive a modified Haber-Weiss (Fenton) reaction that results in production of the toxic hydroxyl radical (OH^-) from H_2O_2 and O_2^-. These reactions result in lipid peroxidation, which is prevented by incubation of asbestos with the iron chelator, desferroxamine (*43*).

At high concentrations, AOS are cytotoxic to cells of the respiratory tract, but at low concentrations they induce functional changes in rodent lung fibroblasts that may be critical to the pathogenesis of asbestos-induced fibrotic lung disease. For example, after addition of xanthine and xanthine oxidase (a chemical generating system producing O_2^-), rat lung fibroblasts in vitro produced increased amounts of cell-associated collagen in a pattern similar to that observed after their exposure to crocidolite asbestos (*40, 44*). In an inhalation model of rapid-onset asbestosis, osmotic pumps containing polyethylene glycol (PEG)–conjugated catalase, the enzyme scavenging H_2O_2, were implanted subcutaneously into rats before they were exposed to crocidolite for 20 days (*45*). This procedure boosted 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. This study was the first successful experimental approach to the prevention of asbestos-associated lung disease. Moreover, the results support the concept of a cause and effect relation between AOS and the development of asbestosis.

Mechanisms of Asbestos-Induced Carcinogenesis

Carcinogenesis is a multistage process that classically has been described in two stages (*46*). The "initiation" stage corresponds to a heritable genetic change (point mutation) induced in a cell by a carcinogenic substance. It is followed by the "promotion" stage, a series of events in which the initiated cell undergoes proliferative and genotypic changes conferring the malignant phenotype. During the past few years, the identification of a number of proto-oncogenes has resulted in a new understanding of the successive genetic events involved in the process of malignant transformation. Increased expression of these genes may cause the production of growth factors or growth-factor receptors. Loss of other genes (anti-oncogenes) also appears to contribute to the carcinogenic process. These findings indicate that the distinction between genetic and epigenetic events in carcinogenesis is not simple, especially because chromosomal rearrangements or deletions associated with point mutation and activation or loss of genes can happen at any stage in the process of cell transformation.

Whether the multistage model is directly applicable to asbestos-associated carcinogenesis is unclear. Unlike most carcinogens, asbestos does not cause base substitution and frameshift mutations in bacterial-mutation assays (*47*). Of the 23 agents designated as group 1 human carcinogens by the International Agency for Research on Cancer (IARC), only asbestos and conjugated estrogens were nongenotoxic as defined by both the Ames test and rodent bone-marrow assays for detection of chromosomal aberrations or micronucleated erythrocytes (*48*). Although asbestos was weakly mutagenic in Chinese hamster lung cells (*49*), it was not mutagenic in liver epithelial cells or in Syrian hamster embryo (SHE) fibroblasts (*50*). Asbestos did not cause morphologic transformation of C3H 10T1/2 cells (*51*), but transformed both BALB/c#3T3 and SHE fibroblasts (*52*). Glass fibers and nonfibrous silica (albeit at much higher concentrations) also were active in the SHE bioassay. In this system, longer, thinner fibers were more potent in the induction of transformation and chromosomal anomalies, an observation consistent with the increased malignant potential of these fibers in comparison to shorter fibers or particles after their administration intrapleurally, intraperitoneally, or by inhalation to rodents (*29, 30*).

In these and other in vitro studies, the biologic effects of fiber types have been assessed comparatively on a mass (milligrams of fibers per dish) rather than a numerical (numbers of fibers of a given size per dish) basis. Cytotoxicity and cytogenetic effects of chrysotile, crocidolite, and erionite (an aluminosilicate fiber) recently were compared in Chinese hamster lung fibroblasts (V79 cells) (*53*). Numbers of chrysotile fibers required to produce cytotoxic or cytogenetic changes were several orders of magnitudes higher in comparison to erionite, the most potent fiber, or crocidolite, a fiber of intermediate potency. These results are consistent with the higher tumorigenic potential of erionite in rodent inhalation experiments (*54*).

In some studies, asbestos appears to augment the mutagenic and carcinogenic effects of chemical carcinogens and radiation. For example, both crocidolite and chrysotile increased the frequency of mutation and transformation in rodent epithelial cells and fibroblasts exposed to benzo[*a*]pyrene (BaP) (*50*) and radiation or radon

alpha particles (*51*). However, synergistic effects of asbestos and BaP were not observed in two studies with SHE and rat mesothelial cells, respectively (*52, 55*).

The particulate nature of asbestos and its capacity to bind nucleic acids has prompted transfection studies in which asbestos was used as a vehicle for introducing DNA or RNA into a number of cell lines (*56*). Under these circumstances, asbestos was intermediate in rank in comparison to a number of other insoluble facilitators including calcium phosphate, talc, and kaolin, none of which have been associated with the induction of cancer.

After addition to human or rat mesothelial cells, both chrysotile (in rats) (*57*) and amosite (in humans) (*58*) have caused aneuploidy and altered growth characteristics after repeated passaging. Injection of rat mesothelial cells into nude mice after a single exposure to chrysotile did not cause tumors in animals, but multiple exposures (36 times) to chrysotile and repeated passaging resulted in tumorigenic cell populations (*57*). In contrast, human mesothelial cells displaying chromosomal abnormalities and growth alterations after duplicate exposures to cytotoxic concentrations of amosite were not tumorigenic in nude mice (*58*). Asbestos promoted the proliferation of mesothelial cells both in organ cultures of human mesothelium exposed to asbestos in vitro and in mice given intraperitoneal injections of asbestos (*59*).

Asbestos fibers come in contact with the chromosomes of rat mesothelial cells (*60*) and the mitotic apparatus of V79 (*53*) and SHE (*61*) cells in vitro. These interactions might induce chromosomal misaggregation or abnormalities. Several investigators have examined chromosomal aberrations in human mesotheliomas, but changes appeared inconsistent from tumor to tumor. The most common abnormalities involved inversions, translocations, and deletions of chromosomes 1, 3, 7, 9, 17, and 22 (*62*). Constitutively enhanced expression of the PDGF-B gene, the proto-oncogene c-*sis*, was observed in human mesothelioma cell lines when compared to normal human mesothelial cells (*63*).

In comparison to human mesothelial cells, human bronchial epithelial cells in vitro are relatively resistant to asbestos. In one study, concentrations of chrysotile, crocidolite, or amosite asbestos approximately ten times as high as that required for mesothelial cells were required to achieve a comparable increase in toxicity (as measured by a 50% decrease in colony-forming efficiency of human bronchial epithelial cells) (*64*). In another study, aneuploidy was not increased significantly over a range of concentrations of either crocidolite or chrysotile asbestos (*65*). This latter observation and the demonstration that insertion of asbestos into rat tracheal grafts can cause the development of carcinomas following insertion of subcarcinogenic amounts of the polycyclic aromatic hydrocarbon, dimethylbenzo[*a*]anthracene (*66*), suggest that asbestos is a promoter in the development of lung cancers. In support of this concept, both crocidolite and chrysotile asbestos induced a number of biochemical and proliferative alterations in both rodent and human tracheal epithelial cell and organ cultures that were similar to those observed in mouse skin that had been treated with the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (*67*). The repertoire of these asbestos-associated proliferative changes, which were masked in tracheal epithelial cells in a high-serum containing medium or by addition of transforming growth factor–type B (TGF-β_1) (*68*), included enhanced incorporation of ^{3}H-thymidine, increases in colony-forming efficiency, and the development of squamous metaplasia, that is, conversion of differentiated mucociliary cells to keratinizing cells resembling epidermis. Induction of ornithine decarboxylase (ODC), a rate-limiting enzyme in the biosynthesis of polyamines that is increased in mouse skin after exposure to TPA but not after addition of nontumor promoting phorbol derivatives, also occurred in a dosage-dependent fashion in tracheal epithelial cells exposed to long, thin, asbestos and glass fibers. In contrast, nonfibrous particles and shorter fibers did not increase ODC activity at similar concentrations (*69*).

Until quite recently, it was unclear how asbestos triggered proliferation in tracheal epithelial cells. However, several pieces of data suggest that mechanisms of cell signaling 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 phosphoinositide signal-transduction pathway (*70*). Mitogenic concentrations of crocidolite asbestos caused increased accumulation of diacylglycerol in tracheal epithelial cells (*71*) and subsequent activation of PKC (*72*), 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 ODC activity in tracheal epithelial cells by inhibitors of PKC and calcium channel antagonists (*69*) suggests that PKC is related causally to asbestos-associated cell proliferation.

Mechanisms other than tumor promotion by asbestos also may explain interactions between smoking and asbestos; these mechanisms could be important in the development of lung cancers in asbestos workers (*7, 73*). For example, smoking impaired clearance of amosite asbestos from rodent lungs and increased retention of fibers in airway epithelial cells (*74*). Both cigarette smoke and asbestos induced AOS in a synergistic fashion in vitro and damaged isolated bacteriophage DNA (*75*). AOS liberated from asbestos fibers also catalyzed the oxidation of 6-hydroxybenzo[*a*]pyrene to a more mutagenic and carcinogenic radical (*76*). Because crocidolite and chrysotile asbestos adsorbed BaP and acted as vehicles to increase both uptake of these lipophilic carcinogens and formation of DNA adducts in tracheal epithelial cells (*77*), fibers might facilitate the initiation of lung tumors by BaP.

Public Policy

The available experimental and epidemiological data indicate that both fiber type and size are important determinants of the pathogenicity of asbestos. Although asbestos has caused disease in the workplace (*78*) and such occurrence has resulted in calls for regulations to protect workers (*79*), recent epidemiologic data are concordant with the suggestion that exposure to chrysotile at current occupational standards does not increase the risk of asbestos-associated diseases (*17, 21, 27, 28*). Unlike most other countries, particularly in the European community, which have more stringent requirements for regulation and importation of amphiboles, federal policy in the United States does not differentiate between different types of asbestos.

Does airborne asbestos present a risk to the health of individuals in schools and other buildings? The available data do not indicate that asbestos-associated malignancies or functional impairment will occur as a result of exposure to most airborne concentrations of asbestos in buildings. First and foremost, the levels of airborne asbestos in buildings, even with damaged ACM, are magnitudes lower than concentrations in the unregulated workplace in the past and approximately 1/100 of the permissible exposure of 0.2 fibers per cubic centimeter of air in the U.S. workplace (*80*). Before the enforcement of occupational standards, workplace concentrations of 100 or more fibers per cubic centimeter of air were not uncommon (*81*). In contrast, surveys of asbestos in schools and public buildings show that the mean airborne concentrations are several thousand–fold lower (Table 1). With few exceptions, the type of asbestos fiber found predominantly in buildings is chrysotile. Accumulating evi-

dence indicates that this asbestos type is probably not associated with the occurrence of mesotheliomas at low levels of exposure. For example, recent analyses on the fiber concentrations in lungs of asbestos workers showed that chrysotile workers with mesothelioma had 400 times the median lung fiber burden in comparison to workers exposed to amphiboles. Data indicate that mesotheliomas in chrysotile workers appeared at lung burdens comparable to that required for the development of asbestosis, a disease associated with occupational exposure to asbestos in the past unregulated workplace (*82*).

Transmission electron microscopy of air samples is essential for the identification and quantitation of finer asbestos fibers. In the United States and United Kingdom, the direct transmission electron microscopy method is advocated to determine airborne asbestos fiber concentrations in buildings. In France, the indirect transmission electron microscopy technique is used, and concentrations are expressed on a mass (milligram) basis. The limit for detection of fibers by phase-contrast microscopy is approximately 0.01 fibers per cubic centimeter of air, a concentration higher than that reported in most schools and buildings (Table 1). Moreover, phase-contrast microscopy cannot be used to identify types of fibers (asbestos or nonasbestos) or to detect fibers less than 0.5 μm in diameter, twice the diameter of fibers associated with the greatest biological activity and induction of tumors in rodents (diameters ≤0.25 μm, that is, Stanton fibers) (*29, 30*). Such long, thin asbestos fibers are rarely found in air samples of buildings (*81, 83*). As shown in Table 1, fiber concentrations from recent studies in buildings are comparable to levels in outdoor air, a point surely relevant to assessing the health risks of asbestos in buildings. Airborne concentrations of asbestos in buildings reported in the 1970s were somewhat higher, presumably because of earlier, less sophisticated sampling and analytical techniques.

Recent epidemiologic studies of deaths from mesothelioma in the general population also suggest that risk from asbestos in buildings is miniscule (*9, 10, 84*). In comparison to lung cancers (an average of 130,000 cases per year in the United States, largely attributed to smoking), an estimated 1,500 cases of mesothelioma per year occur in the U.S. population (*85*). The data on death rates from pleural or peritoneal mesotheliomas over the past 10 to 20 years indicate that mesotheliomas are increasing in males over 65 years of age who have a past occupational history of exposure to asbestos (*84*). By contrast, death rates from mesothelioma in females of all ages have declined slightly or remained constant. These results support the concept that asbestos in buildings is not an important risk factor, as one would expect increased mesotheliomas in both males and females in this case. A recent French study did not show increased risks of asbestos-associated malignancies, pleural plaques, or functional impairment of the lung (effects clearly present in asbestos workers) in persons exposed for 10 years to airborne asbestos in buildings (*86*). Although this survey is still in progress, no mesotheliomas have been observed to date among approximately 15,000 permanent occupants.

Although the validity of extrapolating from high to low dose levels has never been confirmed empirically in the evaluation of asbestos, calculated lifetime risks from mesotheliomas and lung cancers attributable to asbestos in schools and other buildings have appeared in recent years (*85, 87*). The linear dose-response equations in these models have been used with the assumption that there is no threshold for disease, a hypothesis which is open to question. Moreover, the range of estimated risks varies from study to study. With the exception of one analysis (*85*), differences between the pathogenic potential of chrysotiles and amphiboles have not been considered in these assessments, and the importance of fiber size has been ignored. Regardless, examination of combined data from published risk estimates shows that risks of asbestos-related total deaths (both lung cancers and mesotheliomas) due to exposure in schools are magnitudes lower than commonplace risks in modern-day society (Table 2).

Table 2. Estimates of risk from asbestos exposure in schools in comparison to other risks in U.S. society. Data from six published risk estimates (*87*) in which total deaths (lung cancer and mesotheliomas) attributable to asbestos exposure over a lifetime were estimated per 1 million students exposed to 0.00024 fibers per cubic centimeter air (the mean airborne concentration in schools, Table 1) for five school years, beginning at age 10. Estimates indicate that the annual rate is 0.005 to 0.093 deaths per million students for an average life expectancy of 75 years. Modified with permission from Weill and Hughes (*90*).

Cause	Annual rate (deaths per million)
Asbestos exposure in schools	0.005 to 0.093
Whooping cough vaccination (1970 to 1980)	1 to 6
Aircraft accidents (1979)	6
High school football (1970 to 1980)	10
Drowning (ages 5 to 14)	27
Motor vehicle accident, pedestrian (ages 5 to 14)	32
Home accidents (ages 1 to 14)	60
Long-term smoking	1200

The AHERA ruling of 1986 brought asbestos to the attention of the U.S. public and instilled fears in parents that their children would contract asbestos-related malignancies because of high levels of airborne asbestos fibers in schools. Panic has been fueled by unsupported concepts such as the "one fiber theory," which maintains that one fiber of inhaled asbestos will cause cancer. As a result of public pressure, asbestos often is removed haphazardly from schools and public buildings even though most damaged ACM is in boiler rooms and other areas which are inaccessible to students or residents (*1*). The removal of previously undamaged or encapsulated asbestos can lead to increases in airborne concentrations of fibers in buildings, sometimes for months afterwards (*83*), and can result in problems with safe removal and disposal. Asbestos abatement also has led to the exposure of a large new cohort of relatively young asbestos removal workers. While these people should be protected by careful regulation of the circumstances of removal, they are often exposed under suboptimal working conditions.

As a result of the AHERA ruling, public and private schools are required to inspect for asbestos and inform parents if ACM are present. Although the law does not require or set standards for the removal of asbestos, schools, often with little expert advice, must submit a management plan detailing how they will deal with damaged asbestos and can be fined a maximum of $5000 per day for lack of compliance to deadlines. The EPA has recommended bulk sampling of ACM to determine the presence of asbestos and visual inspection to determine the course of action, rather than measurement of airborne levels of fibers—data that are far more important in determining the need, if any, for removal of ACM.

The available data and comparative risk assessments (Table 2) indicate that chrysotile asbestos, the type of fiber found predominantly in U.S. schools and buildings, is not a health risk in the nonoccupational environment. Clearly, the asbestos panic in the U.S. must be curtailed, especially because unwarranted and poorly controlled asbestos abatement results in unnecessary risks to young removal workers who may develop asbestos-related cancers in later decades. The extensive removal of asbestos has occurred less frequently in Europe.

Prevention (especially in adolescents) of tobacco smoking, the principal cause of lung cancer in the general population, is both a more promising and rational approach to eliminating lung tumors

than asbestos abatement. Even acknowledging that brief, intense exposures to asbestos might occur in custodians and service workers in buildings with severely damaged ACM, worker education and building maintenance will prove far more effective in risk prevention for these workers.

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Priming and Human Memory Systems

ENDEL TULVING AND DANIEL L. SCHACTER

Priming is a nonconscious form of human memory, which is concerned with perceptual identification of words and objects and which has only recently been recognized as separate from other forms of memory or memory systems. It is currently under intense experimental scrutiny. Evidence is converging for the proposition that priming is an expression of a perceptual representation system that operates at a pre-semantic level; it emerges early in development, and access to it lacks the kind of flexibility characteristic of other cognitive memory systems. Conceptual priming, however, seems to be based on the operations of semantic memory.

MEMORY WAS TRADITIONALLY THOUGHT TO BE A UNITARY faculty of the mind. Recently, however, many researchers have adopted the hypothesis that memory consists of a number of systems and subsystems with different operating characteristics. The problem of what these systems and their properties are, and how they are related to one another, now occupies the center stage in research on memory.

One broad, as yet tentative, organizational scheme distinguishes procedural, semantic, and episodic memory (*1*). Procedural memory underlies changes in skillful performance and appropriate responding to stimuli; semantic memory has to do with acquisition and use of factual knowledge in the broadest sense; and episodic memory enables people to remember personally experienced events. The domain of procedural memory is behavior, whereas that of semantic and episodic memory is cognition or thought. Cognitive memory systems have the capability of modeling the external world—that is, of storing representations of objects, events, and relations among them—whereas procedural memory does not have this capability.

Evidence is accumulating about yet another category of learning and memory, one that is not procedural, semantic, or episodic. It has come to be known as priming (*2*). Its function is to improve identification of perceptual objects. Priming is a type of implicit memory; it does not involve explicit or conscious recollection of any previous experiences. It has affinities to both procedural and semantic memory. Priming resembles procedural memory in that it enhances perceptual skills. It also resembles semantic memory in that it involves cognitive representations of the world and expresses itself in cognition rather than behavior.

The prototypical priming experiment consists of two stages. In the first (study) stage, the subject is presented with a stimulus object (target). Target stimuli may comprise words, line drawings of objects, drawings of faces, and the like. In the second (test) stage, which may follow the first after an interval that can vary from seconds to months, the subject is given reduced perceptual information about the object and asked to name or categorize it. Reduced cues may consist of initial letters or graphemic fragments of words, partially obliterated words or figures, originally presented faces in a more highly schematized form, or tachistoscopic presentation of stimuli. Priming is said to have been demonstrated if the probability of the identification of the previously encountered targets is increased, or the latency of the identification response is reduced, in comparison with similar measures for nonstudied control items. The difference between performance on the target items and the nonstudied items provides a measure of the magnitude of the priming effect.

Although priming and other kinds of implicit memory have been reported from time to time, systematic attempts to explore it began about 10 years ago (*3*). One of the triggers for the study of priming turned out to be experiments by Warrington and Weiskrantz (*4*) showing that densely amnesic patients, who were severely impaired in their ability to remember recently seen information, exhibited near-normal learning when they were tested by methods that tapped what we now know is priming. A second stimulus for the study of priming lay in research concerned with the nature of and access to lexical representations (*5*). A third source of influence was the growing interest in the classification of memory into distinctive categories such as episodic and semantic memory (*6*) and procedural and declarative memory (*7*).

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