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Mechanisms of Asbestos Carcinogenicity

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ABSTRACT

We present a brief review of different potential mechanisms at the molecular and cellular levels that may be involved in asbestos-induced carcinogenicity. The usefulness of considering such mechanisms in developing appropriate biologically based models to estimate carcinogenic risk at environmental levels of asbestos fibers is discussed.

INTRODUCTION

ASBESTOS IS A GENERAL COMMERCIAL name for a group of mineral fibers of hydrated silicates with a variety of physical characteristics and metal compositions.[1] Occupational exposure to several types of asbestos fibers has been shown to have a causal relationship with the development of lung cancer and malignant pleural mesotheliomas.[2,3] However, animal studies have shown that morphological difference and size can result in different carcinogenic potencies.[4–6] Initially, workplace exposure to asbestos fibers was the primary concern for human health hazards; however, more recently, attention has turned to potential risks to the general public exposed to asbestos used in building materials in the construction of schools and public and commercial buildings. There is a likely potential to release high fiber concentrations into the environment during the removal of asbestos from these buildings in order to reduce long-term asbestos exposures. Costs for removal have been estimated to be greater than 53 billion dollars.[7] Therefore, it is important to have the most accurate estimates of carcinogenic risks in making decisions whether removal is necessary and would actually result in an adequate reduction in risk.

Regulatory agencies are obligated by law to protect the public from levels of carcinogens that would pose an unreasonable risk to people. This often involves using epidemiological studies in which cancers have been observed to be statistically elevated in an exposed population in comparison to an unexposed matched population and extrapolating to lower levels where the "acceptable" risk of cancer would be in the order of 1 out of 10^5 or 10^6. Although most epidemiological studies are inadequate for precise quantitative extrapolations, without better alternatives they are used to set environmental exposure limits for carcinogenic agents. In conducting such assessments, however, no information is used concerning the mechanisms by which carcinogens cause normal cells to become carcinogenic. Conservative, and possibly inaccurate, assumptions are made by assuming that the induction of cancer can result from one interaction or "hit" with DNA, that there is a linear relationship between external exposure and the number of interactions with DNA, and that there is no "safe" exposure level where the probability of causing cancer is zero. In 1986, the EPA used epidemiological studies and these assumptions to estimate that a lifetime exposure to 0.0001 fibers of asbestos per ml of air would result in 2.4 asbestos-associated deaths from lung cancer and mesothelioma per 100,000 people exposed.[8] However, the accuracy of using such linear models to extrapolate to lower levels of asbestos exposures has not been verified in epidemiology studies, nor has there been any biological data that would indicate that asbestos-induced carcinogenicity is a simple "one-hit" mechanism.

In the past two decades, many scientific studies revealed the complex nature of interactions of asbestos with macromolecules and cellular responses to asbestos exposures. These interactions can result in direct and/or indirect

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damage to DNA, and may cause initiation events (mutations) which may cause cell transformation and eventually lead to cancer. Initiation is only one part of the carcinogenesis process; however, agents such as asbestos[9,10] also can act as cocarcinogens or promoters which reduce the time necessary for an initiated or transformed cell to develop into a cancer cell. Here, we propose several biological mechanisms as to how asbestos fibers may initiate and promote cancer at the molecular level. However, sufficient quantitative information is not yet available to use these mechanisms to develop more biologically based risk assessment models. Our intent is to identify and describe molecular mechanisms based on current studies and to provide stimulus to generate additional data useful for more accurate quantitative estimate of asbestos carcinogenicity.

In addition to biological mechanisms, other factors are also important in assessing the carcinogenic risk of exposure to asbestos fibers. These other factors include the pharmacokinetics of asbestos deposition in lung and pleural tissues, accumulation and elimination, target cell specificity, and physicochemical properties of the different asbestos fibers. Here we focus only on the potential mechanisms at the molecular and cellular levels.

EVIDENCE FOR DIRECT GENOTOXIC ACTIVITY

Initiation events are the results of permanent alterations of DNA expression caused by gene mutations (alteration of single bases in DNA or deletions within one gene); chromosomal alterations, such as deletions of many genes or rearrangements of chromosomes where part of one chromosome is translocated to another chromosome; and numerical alterations that occur during cell division where daughter cells receive abnormal distributions of chromosomes. Depending upon what genes these events affect, the cell carrying the aberrations can die or survive as a normal cell, or if oncogenes or regulatory genes are involved, the cell can survive without the capability to differentiate, to control its growth, and to function normally.

In vivo studies have shown that crocidolite asbestos fibers of mixed sizes can be engulfed by mice peritoneal macrophage cells after an interperitoneal injection and physically interact with skeletal cellular proteins[11] and, therefore, may have access to the genetic material within the cell. Brody et al.[12] also have reported that inhaled chrysotile asbestos fibers are taken up by pulmonary epithelial cells of rats and then can associate with intracellular actin-containing microfilaments, and therefore have the capacity to bind to protein polymers that are involved in chromosomal separation during cell division. Both crocidolite and chrysotile asbestos fibers (the majority of fibers were less than 5 μm in length and between 0.1 and 1.0 μm in diameter) injected into the pleural cavity of guinea pigs have been shown to penetrate mesothelial cells within two weeks after exposure.[13] These findings demonstrate that asbestos fibers can enter cells in vivo and have access to cytoplasmic macromolecules and potentially can interact with DNA.

Many in vitro studies also have been conducted with asbestos fibers. Haugen et al.[14] reported that human bronchial epithelial cells were capable of engulfing amosite asbestos fibers and fibers within the cytoplasm appeared free or in membrane-bound vacuoles. They also reported that intranuclear amosite inclusions occur in human bronchial epithelial cells. Cultured rat mesothelial cells can phagocytize chrysotile A asbestos fibers[15] having a mean fiber length of less than 4 μm, and both chrysotile A and crocidolite asbestos fibers ranging in lengths from more than 10 μm to 1 μm and from more than 1 μm to less than 0.1 μm in diameter have been shown to adhere to chromosomes in metaphase and cause polyploidy.[16] In rat mesothelial cells, chrysotile asbestos fibers having a mean length of less than 4 μm with 84% of the fiber having a diameter of less than 0.058 μm, caused chromosomal aberrations that were predominantly chromatid breaks as well as polyploidy.[17] Exposure of human pleural mesothelial cells to amosite asbestos fibers induced aneuploid cells that exhibited altered growth characteristics,[18] although isolated aneuploid clones were not found to be tumorigenic when injected into athymic nude mice. Hesterberg et al.[19] reported that Syrian hamster embryo cells internalized chrysotile asbestos fibers and, in some instances, chromosomes appeared to be wrapped around individual asbestos fibers. In another study, Syrian hamster embryo cells arrested at G_1/S and exposed to asbestos fibers caused a 22-fold increase in displaced chromosomes over control cultures. Hesterberg et al.[19] postulated that the missegregation could have been caused by direct physical interference with chromosomes preventing or hindering their separation during cell division and/or interacting with proteins (tubulin) that form the spindle apparatus for chromosomal separation during cell division. Similar findings were reported for cultured Chinese hamster cells.[20–22] However, Sincock et al.[22] reported that no significant chromosome damage was observed in primary human fibroblast cells from skin and

lung or in human lymphoblastoid cell lines exposed to either crocidolite or chrysotile asbestos fibers with mean particle lengths of 1.1 to 3.4 μm and mean diameters between 0.15 and 0.47 μm. Fornace[23] was unable to detect single-strand DNA breaks in human fibroblast cells that had been treated with amosite asbestos fibers at doses of low cellular toxicity. Mossman et al.[24] have also shown that crocidolite and chrysotile asbestos fibers at nontoxic levels did not cause single-strand breaks in the DNA of hamster tracheal epithelial cells. Libbus et al.[25] demonstrated that crocidolite asbestos fibers of average length and diameter of 14.8 μm and 0.9 μm, respectively, caused single-strand DNA breaks in cultured rat embryo cells. These investigators used a nick translation assay rather than alkaline elution to measure breaks. Electron microscopic examinations of the treated cells indicated that strand breaks occurred both in cells that visibly contained fibers and in cells where no fibers were detected. The DNA damage appeared to be dose related but nonlinear.

These studies show that asbestos fibers can enter cells, bind to molecular components, and cause chromosomal damage and numerical chromosomal aberrations in certain cell types by direct interaction or indirectly through some intermediate that can result in mutations. Asbestos apparently causes severe chromosomal damage rather than alterations in just single genes since asbestos fibers have not been shown to cause gene mutations in mammalian cell[26,27] or in bacterial cell[28] test systems or stimulate unscheduled DNA synthesis in rat hepatocytes.[29] However, Yang et al.[30] have demonstrated that xeroderma pigmentosum fibroblast cell lines, deficient in excision repair of certain types of chemical or ultraviolet light-induced DNA damage, are more sensitive to chrysotile, amosite, and crocidolite asbestos fibers than normal human fibroblasts. These findings suggest that some types of asbestos-induced DNA damage may involve small lesions that are reparable.

Asbestos fibers (amosite, anthophyllite, crocidolite, Rhodesian A chrysotile, and Canadian B chrysotile) have been shown to facilitate the transfection of viral DNA into liver epithelioid cells from chimpanzee livers, rhesus monkey kidneys cells, human carcinoma, and NIH 3T3 mouse fibroblast cells.[31] However, the concentration of asbestos fibers needed to cause transfections was high (3–10 mg/ml). A linear dose-response relationship was observed at higher doses, but at 0.1 mg/ml, little or no transfection was seen. Appel et al.[32] also were able to introduce plasmid DNA vectors into *cos*-7 monkey cells using Canadian chrysotile sample B asbestos fibers with an average diameter of 7 μm and lengths in the range of 130–3 μm as the transfecting agent. Therefore, under experimental conditions using high concentrations of asbestos fibers, nucleic acids can be inserted into the genome of cells. Ke et al.[33] successfully transfected normal human mesothelial cells with fragmented DNA from a transformed human mesothelial cell line and obtained transformed clones that were morphologically indistinguishable from the original transformed line. Hence, the inserted DNA can alter the expression of cellular oncogenes and antioncogenes, depending on the insertion sites, or the transfected DNA could itself possess oncogenes that may be translated after insertion into genomic DNA.

EVIDENCE FOR INDIRECT GENOTOXICITY

There are two potential mechanisms where asbestos fibers can cause the formation of reactive oxygen species. These reactive oxygen species, in turn, can act as second messengers in causing genotoxicity. One mechanism involves the transfer of electrons from asbestos fibers (chrysotile with mean fiber length of 6 μm) to cellular molecules which, in turn, can interact with DNA.[34] The second mechanism involves an asbestos-induced inflammatory response that causes the accumulation of macrophages and polymorphonuclear leukocytes, which can release active oxygen species such as superoxide free radical and hydrogen peroxide, which then interact with DNA to cause mutations.[35–38]

Wong et al.[39] suggested that the ferrous iron in certain asbestos fibers may reduce oxygen to form the superoxide free radical. The superoxide anion may then result in the formation of other reactive oxygen species such as hydrogen peroxide and the hydroxyl free radical. Eberhardt et al.[40] and Weitzman and Graceffa[41] have shown that asbestos fibers can catalyze the formation of both the superoxide radical and hydroxyl radical from hydrogen peroxide. Mossman et al.[38] reported that asbestosis in rats caused by inhaling crocidolite asbestos fibers could be inhibited if the animals also were given catalase, which converts hydrogen peroxide into water. Cytotoxicity of hamster tracheal epithelial cells induced by crocidolite and chrysotile asbestos fibers of lengths varying from > 10 μm to < 2 μm can be inhibited by superoxide dismutase, which converts superoxide radical to H_2O_2, and by hydroxyl radical scavengers.[42] Catalase was ineffective in protecting the cells from asbestos

toxicity, but mannitol and dimethylthiourea, both scavengers for the hydroxyl free radical, were very effective in reducing cell toxicity. Hydrogen peroxide is required to generate the hydroxyl radical; it is surprising therefore that catalase did not have a protective effect. Like superoxide dismutase, catalase is not likely to penetrate the cell wall. One explanation may be that hydrogen peroxide is not formed at outer membrane surfaces but superoxide anion is. Unlike catalase and superoxide dismutase, mannitol and dimethylthiourea are capable of entering the cell and interacting with hydroxyl radicals. When the exposure time to asbestos was increased, superoxide dismutase activity was induced in the cells.[42]

Fisher et al.[43] reported that heating chrysotile asbestos fibers decreased their binding to bovine serum albumin, but that ionizing radiation could restore the protein-binding capability. The effects of untreated and treated asbestos on cell cytotoxicity and viability of human foreskin fibroblasts and bovine macrophage cells were also analyzed. For both cell types, heat-treated asbestos fibers were less toxic than untreated, radiation-treated, and heat/radiation-treated asbestos. One possible mechanism consistent with these results involves the release or escape of metastable electrons within the mineral and the regaining of activated electrons upon radiation. The toxicity of asbestos may be attributable to the fibers contacting cells and transferring electrons to cell surfaces or, upon entering the cell, electron transfer could occur from asbestos fibers to various biomolecules that cause genetic damage leading to carcinogenesis. Valentine et al.[34] also demonstrated that heat pretreatment of chrysotile asbestos fibers with mean fiber lengths of 6 μm reduced cytotoxicity toward human fibroblast cells and bovine alveolar macrophages and that reactivation of cytotoxic effects resulted when fibers were irradiated with x-rays. Leanderson et al.[44] have demonstrated that the incubation of chrysotile asbestos fibers with 2-deoxyguanosine produced 8-hydroxydeoxyguanosine. This showed that, under laboratory conditions, asbestos has the capability to modify DNA bases through a reaction mediated by hydroxyl radicals. If this reaction occurs in vivo, the altered base could result in genetic damage and mutations.

Moalli et al.[45] have shown that crocidolite asbestos fibers injected into the peritoneal cavity of mice produced an inflammatory response and caused mesothelial cell injury and regeneration. Asbestos fibers were primarily found clustered near the stomata of the lymphatics at the peritoneal surface of the diaphragm. Fibers accumulated at these sites during the first three days after injection and some still remained after 6 months. Hemorrhaging on the peritoneal surface of the diaphragm occurred and there was accumulation of neutrophils and macrophages around the fiber clusters. The inflammatory response, as well as the presence of macrophages at the deposition sites, persisted even after 6 months.

Other studies by Warheit et al.[37] and Brody et al.[46] have shown that inhaled chrysotile asbestos fibers can deposit on alveolar duct bifurcations in the lungs of rats and that pulmonary macrophages accumulate at these deposition sites. Additional studies by Warheit et al.[47] have shown that asbestos fibers enhance pulmonary macrophage chemotactic responses that can result in migration of additional macrophage cells to the asbestos deposition sites. Goodglick and Kane[48] have demonstrated that crocidolite asbestos fibers can induce peritoneal macrophages in mice to produce/release reactive oxygen species such as hydrogen peroxide. Weitzman and Stossel[49] have demonstrated that human phagocytes can cause mutations in bacterial cells by producing reactive oxygen species. Therefore, the continual release of mutagenic reactive oxygen species in vivo and the continual regeneration of "target" cells (e.g., mesothelial cells) in the same vicinity could result in genetic alterations causing some of the mesothelial cells to be transformed.

ASBESTOS AS A CANCER PROMOTER

Topping and Nettesheim[9] demonstrated that chrysotile asbestos fibers promote tumors in F344 rat tracheal transplants in the retroscapular region of 8-week-old isogeneic recipients. Dimethylbenz(a)anthracene (DMBA) was used to initiate the transplanted cells which were then exposed to asbestos fibers at the transplantation site. No carcinomas were found in animals given only DMBA or in animals exposed only to asbestos. However, using both initiator (25 μg) and promoter (200 μg), the carcinoma incidence increased to 9/40 (23%). A previous study[50] showed that an asbestos concentration of 2000 μg was required to get a 5% increase in the incidence of tracheal carcinomas without any initiation.

Topping and Nettesheim[51] reported that tracheal carcinogenesis in rats was also enhanced by 12-*O*-tetradecanoylphorbol-13-acetate (TPA), the well-known tumor promoter in skin, but when given alone was not

capable of initiating a cancer response. Like asbestos fibers, phorbol esters stimulate the production of reactive oxygen species and induce DNA strand breaks,[52,53] and as with asbestos, the toxic responses, as well as the promotional activity of TPA, can be inhibited by antioxidants.[54] Phorbol esters have been studied extensively with respect to their carcinogenic promotion activity[52,54-56] and they have been shown to cause changes in cell membranes, generate reactive oxygen species, increase lipid peroxidation, elevate certain enzyme activities, enhance phospholipid synthesis, alter methylation of macromolecules, and cause chromosomal damage. Promoters may act initially through interactions with cell membranes and stimulate lipid peroxidation, which in turn, through various intermittent steps, produce free radical species that reach and damage genetic material.[57,58] Yano[59] has demonstrated that chrysotile and crocidolite asbestos fibers can induce the formation of malondialdehyde, a product of free radical-induced lipid peroxidation in human polymorphonuclear neutrophil cells, guinea pig peritoneal macrophages, and alveolar lavage cells.

Weinstein[56] has reviewed the current status of the effects of TPA on protein kinase C (PKC). PKC plays a key role in cell signal transduction involving activation of oncogenes, cellular growth, and tumor promotion. PKC is the primary receptor for TPA and the phorbol ester binds at an allosteric site on the enzyme, enhancing its ability to phosphorylate protein substrate(s). Cox et al[60] have reported that PKC phosphorylates a NADPH oxidase on the plasma membrane that catalyzes the reduction of oxygen to the superoxide anion. PKC stimulation also increases the levels of ornithine decarboxylase (ODC), which is the rate-limiting enzyme in the biosynthesis of polyamines that are necessary for the initiation of cell division. Marsh and Mossman[61] have shown that chrysotile and crocidolite asbestos fibers also induce ODC activity in cultured hamster tracheal epithelial cells, but that ODC activity is significantly reduced when calcium entry antagonists (verapamil or nifedipine) are added to the cultures. They found that the longer fibers were more effective in stimulating enzymatic activity. Furthermore, palmitoyl carnitine and 1-(5-isoquinolinylsulfonyl)-2-methylpiperazine, inhibitors of PKC, also were effective in blocking ODC activity that was stimulated by asbestos fibers. It seems unlikely that asbestos fibers are promoting cells, creating active oxygen species, and stimulating enzymes like ODC in a similar manner to TPA. TPA can bind directly to PKC and activate the enzyme. However, asbestos fibers are likely to interact at the plasma membrane, to cause an influx of calcium into the cell, which activates PKC and may stimulate membrane phospholipases.[62] The phospholipases hydrolyze membrane polyphosphatidylinositols to form diacylglycerol and inositol 1,4,5-triphosphate. Diacylglycerol is an activator of PKC[63] and inositol 1,4,5-triphosphate causes release of intracellular stores of calcium.[64] Both calcium and diacylglycerol bind at the regulatory site of PKC and induce a conformational change that enhances the catalytic activity of the enzyme. Roney and Holian[62] have examined the effects of the PKC inhibitors (fluphenazine or staurosporine) on blocking the production of superoxide anion production by chrysotile asbestos fibers and the promoter, phorbol 12,13-dibutyrate, in guinea pig alveolar macrophages. These PKC inhibitors all reduced the amount of superoxide anion production. The authors postulated that asbestos is most likely stimulating membrane phospholipase C to produce diacylglycerol and inositol 1,4,5-triphosphate, which causes an increase in cell calcium levels, which in turn increase the activity of PKC. PKC then is responsible for inducing membrane NADPH oxidase to produce superoxide anion that leads to other reactive oxygen species and causes activation of oncogenes that affect cell growth and differentiation. However, crocidolite, anthophyllite, and amosite did not stimulate the production of superoxide anion as effectively as chrysotile fibers.

Gabrielson et al.[65] exposed cultured human lung mesothelial cells to amosite asbestos fibers and were unable to detect any generation of free radicals, nor did free radical scavengers (glutathione, *n*-acetyl-cysteine, D-alpha-tocopherol, or superoxide dismutase) alter the cytotoxic effects of asbestos. These findings are in contrast to other studies described above. The differences may be due in part to different cell types and experimental conditions as well as to differences in asbestos fiber characteristics.

DISCUSSION

Figure 1 summarizes six potential mechanisms for the induction and promotion of cancer by asbestos fibers. Mechanism 1 involves asbestos fibers penetrating the target cell, directly interacting with DNA, and causing chromosomal aberrations (mutations). Depending on the severity and location of the mutation, some cells will not survive, other cells may survive and continue to function normally, while others may have abnormal expression of

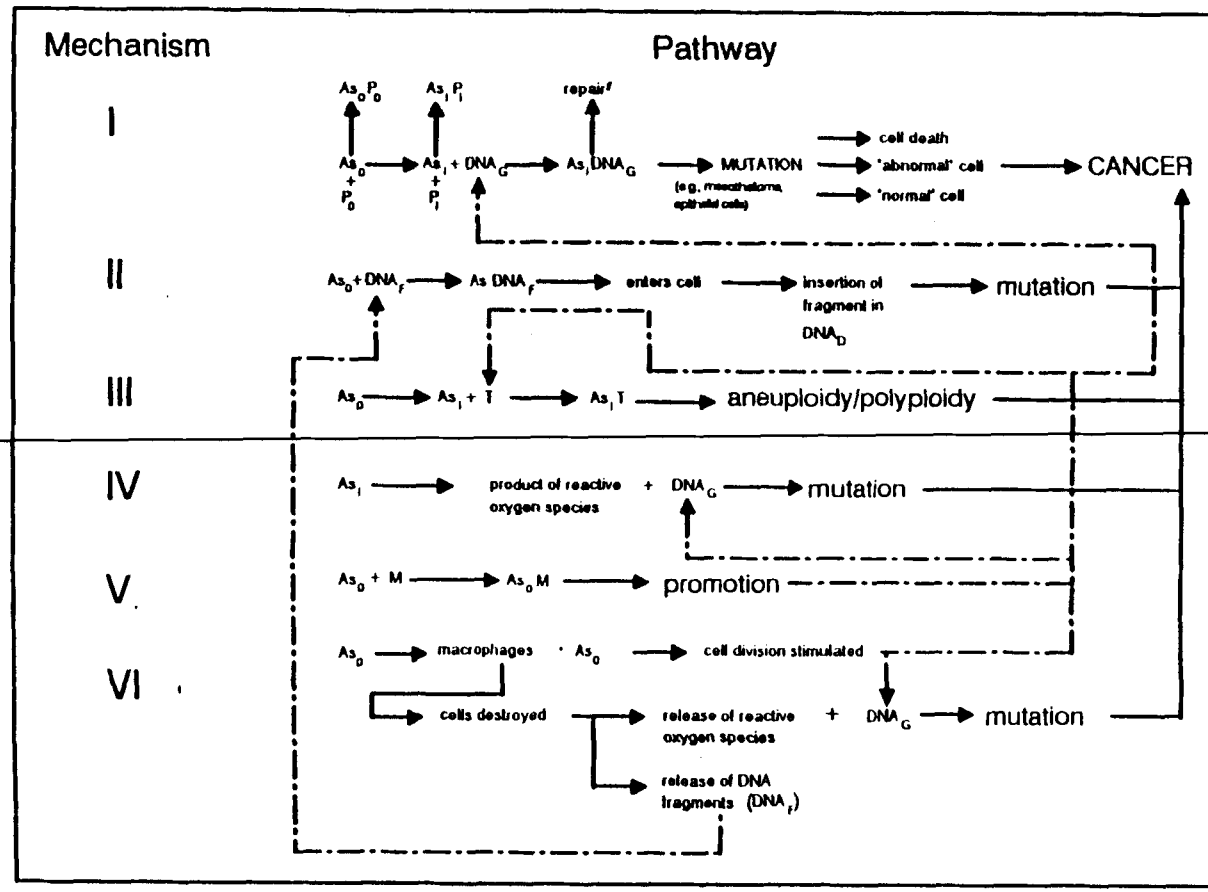

FIG. 1. Different mechanisms for asbestos-induced carcinogenicity. As_o = asbestos fibers outside the cell; As_i = asbestos fibers inside the cell; P_o = protein outside the cell; P_i = protein inside the cell; DNA_G = genomic DNA; DNA_F = fragmented DNA; T = tubulin; M = membrane receptor. See text for further details.

DNA that would constitute the initiation step in the carcinogenic process. Asbestos fibers readily interact with proteins both outside and inside cells. These types of interactions actually may compete with genomic DNA for the asbestos fibers and consequently may serve to protect the cell from asbestos-induced mutations. Because of the many macromolecules available to bind to asbestos fibers, it seems that at low fiber concentrations few, if any, fibers could penetrate the nucleus and interact with DNA.

Mechanism II illustrates the capability of asbestos fibers to interact with DNA fragments and to act as a carrier for the fragments into the cell for insertion into genomic DNA. In vitro experiments with asbestos fibers were done at concentrations of both DNA fragments and asbestos fibers to maximize transformation; it is questionable whether appropriate conditions exist in vivo in which insertion mutagenicity can occur by this process. However, recent findings[66] have shown that DNA fragments exist outside cell membranes and may constitute as much as 1% of total cellular DNA. Furthermore, inflammatory responses induced by asbestos fibers result in the destruction of macrophages and mesothelial cells (Mechanism VI), which can release degraded genomic DNA fragments. Therefore, in vivo DNA fragments are available to bind asbestos fibers that may be inserted into the DNA of normal cells. The likelihood of this mechanism occurring in vivo and contributing to asbestos carcinogenicity at low exposure levels is questionable as the concentrations of both carrier and nucleic acid fragments at asbestos deposition sites may not be sufficient to cause transfection of fragmented DNA into genomic DNA.

Asbestos fibers have been shown to interact with chromosomes and have been proposed to interact with cytoskeletal structural proteins and have been shown to induce aneuploidy and polyploidy. Chromosomal imbalanced cells are abnormal and may be involved in the process of asbestos-induced carcinogenicity. Gibas et al.,[67] Popescu et al.,[68] and Tiainen et al.[69] reported that high incidences of numerical chromosomal abnormalities are present in human mesothelial cells, and the frequencies of certain abnormalities may be nonrandom. Oshimura et al.[70] reported that exposure of Syrian hamster embryo cells to asbestos fibers resulted in a nonlinear dose-dependent increase in aneuploid, tetraploid, and binucleated cells, and that the cytogenic changes, primarily aneuploidy, correlated with cell transformation. Mechanism III in Figure 1 illustrates the binding of asbestos fibers to tubulin, a protein that makes up the spindle apparatus necessary for chromosomal separation during cell division. It is still unclear if chromosomal abnormalities are part of the induction process of asbestos-induced carcinogenicity or whether they may be nonspecific secondary alterations that evolve during the progression of malignant cell growth.

Mechanism IV illustrates that asbestos fibers can transfer electrons to cellular molecules after entering the cell or by interacting at membrane surfaces; the cellular molecules in turn interact with genomic DNA and cause mutations. Mechanism V demonstrates promotional activity of asbestos in which asbestos binds to membrane sites and causes epigenetic effects that initially alter cellular growth and function. These cellular alterations in DNA expression in an already initiated cell (transformed cell) may cause it to progress further toward a cancer cell and may, by stimulating reactive oxygen species, cause a second mutation (transformation) that may be necessary for the formation of a cancer cell. The extent of the promotional response depends upon the number of interactions of asbestos with "receptor" sites (if specific receptor sites exist) on cell membrane surfaces. The kinetics of asbestos binding to membrane "receptors" and the extent of promotional activity are not available, but the kinetics would most likely be nonlinear, and a threshold level needed to stimulate sufficient promotional activity may exist.

The asbestos-induced inflammatory mechanism (VI) is multifaceted in that asbestos fibers attract macrophages, some of which are destroyed and release reactive oxygen species and DNA fragments and cause the release of macrophage growth-stimulating factors that result in cell regeneration at the deposition sites. The release of reactive oxygen species may induce mutations in the neighboring dividing cells; the DNA fragments from destroyed macrophages may bind to asbestos fibers, and become transplanted into nearby cells where the DNA fragments may be inserted into genomic DNA (Mechanism II). The dashed lines in Figure 1 represent the contributing effects that the inflammatory response may have on the other postulated mechanisms by inducing cell division and making more target cells available to be transformed and releasing DNA fragments that could be inserted into genomic DNA.

All six mechanisms presented here potentially could be involved in asbestos-induced mesothelioma and lung cancer and the mechanisms may vary with respect to cell type. Certain mechanisms may realistically occur only at very high concentrations of asbestos fibers and are more likely to occur under in vitro laboratory conditions. Mechanisms V and VI, however, have been demonstrated in vivo, but adequate dose–response relationships for use in quantitative risk assessment are not yet available.

Quantitative cancer risk assessments have always suffered from lack of information on mechanisms of action of

carcinogens, making it necessary to extrapolate to acceptable environmental levels and to assume conservatively that one interaction with DNA will result in the development of a tumor and that tumor incidence is directly proportional to concentration. Enough data are becoming available showing different molecular aspects of asbestos carcinogenicity to design experiments to determine the pertinent molecular mechanisms and dose-response relationships that occur in vivo at environmental exposure levels. This new information can then be used to determine asbestos cancer risks more accurately for regulatory purposes than the current mathematical extrapolation models are capable of doing.

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