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Effects of Fiber Characteristics on Lung Deposition, Retention, and Disease

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There is abundant epidemiologic evidence that asbestos fibers can cause lung fibrosis (asbestosis), bronchial cancer, and mesothelioma in humans, as well as limited evidence for such effects in workers exposed to slag and rockwool fibers. Epidemiological evidence for human disease from inhalation exposures to conventional fibrous glass is negative. While health concerns based on the morphological and toxicological similarities between man-made fibers and asbestos are warranted, it is important to note that most of the toxicological evidence for glass fiber toxicity in laboratory animals is based on nonphysiological exposures such as intratracheal instillation or intraperitoneal injection of fiber suspensions. Man-made fibers have produced lung fibrosis and mesotheliomas in such tests, albeit at much lower yields than asbestos. For all durable mineral fibers, critical length limits must be exceeded to warrant concern about chronic toxicity; i.e., 2 μm for asbestosis, 5 μm for mesothelioma, and 10 μm for lung cancer. Fiber width must be <0.1 μm for mesothelioma, and larger than this limit for asbestosis and lung cancer. The human health risks for most fibrous glass products are either low or negligible for a variety of reasons. First, most commercial fibrous glass products have mean fiber diameters of approximately 7.5 μm, which results in mean aerodynamic diameters approximately 22 μm. Thus, most glass fibers, even if dispersed into the air, do not penetrate into the lung to any great extent. Second, the small fraction of smaller diameter fibers that do penetrate into the lungs are not persistent within the lungs for most fibrous glass products due to mechanical breakage into shorter lengths and overall dissolution. Dissolution is most rapid for the smaller diameters (< 0.1 μm) capable of producing mesothelioma. The greater hazards for slag and rockwools in comparison to glass appear to be related to their smaller diameters and greater durability within the lungs.

Introduction

It is known that the pathogenesis of each of the chronic diseases associated with inhaled fibers is associated with the physical characteristics of the fibers. The evidence is strongest for the amphibole asbestos minerals. In my recent review on asbestos exposure indices (*1*), I showed that asbestosis was most closely related to the surface area of fibers longer than about 2 μm and thicker than about 0.15 μm; mesothelioma to the number of fibers longer than about 5 μm and thinner than about 0.1 μm; and lung cancer to the number of fibers longer than about 10 μm and thicker than about 0.15 μm. The thinner fibers were able to leave the lung and accumulate at pleural and peritoneal sites where mesotheliomas can develop, while the thicker fibers can remain in the lung to initiate lung diseases. The previous review paper discussed the various reasons for the different critical fiber lengths for asbestosis and cancer.

The critical role of fiber dimensions is confirmed by experience with other inorganic fibers that have been shown to be capable of producing asbestosis, mesothelioma, and/or lung cancer in humans or animals. Oregon erionite, a natural zeolite with very thin fibers, produced mesothelioma in virtually all of the rats exposed by inhalation (*2*). Villagers in Turkey living in homes constructed of erionite blocks have very high incidences of mesothelioma (*3*). Fybex, a fibrous potassium octatitinate developed as an asbestos substitute, produced mesothelioma in hamsters exposed by inhalation (*4*) and was abandoned as a commercial product. While man-made mineral fibers (MMMF) containing long-thin fibers are clearly capable of producing fibrosis in animals exposed by intratracheal instillation, and mesothelioma in animals exposed by intraperitoneal injection, the yields are markedly lower than those for asbestos fibers of similar numbers and dimensions. In terms of human experience, the only evidence for chronic disease is among MMMF workers handling rock or slag wool or ultrafine glass fibers during periods when exposures were very high (*5*). For conventional fibrous glass, constituting over 95% of the MMMF usage in the U.S., there is no evidence of chronic disease. As discussed in my recent review (*6*), the much lower order of toxicity for MMMF, in comparison to asbestos, is due to its lesser durability within the lungs. The reasons for the lesser durability of MMMF will be summarized in this review, along with the principal factors affecting fiber deposition patterns and efficiencies, i.e., the aerodynamic properties of the fibers and the nature of convective flow within lung airways.

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Fiber Deposition in the Respiratory Tract

There are five mechanisms that are important with respect to the deposition of fibers in respiratory tract airways. These are impaction, sedimentation, interception, electrostatic precipitation, and diffusion.

Impaction and sedimentation probabilities are governed by the aerodynamic diameter of the fibers which, for long mineral fibers, are close to three times their physical diameters (*7,8*). Most impaction occurs downstream of air jets in the larger airways, where the flow velocities are high, and the momentum of the fiber propels it out of the bending flow streamlines and onto relatively small portions of the epithelial surfaces. Sedimentation, on the other hand, is favored by low flow velocity, long residence times, and small airway size.

Electrostatic precipitation occurs primarily by image forces, in which charged particles induce opposite charges on airway surfaces. It is dependent on the ratio of electrical charge to aerodynamic drag. Little is known about the charge levels on MMMF in the workplace. Jones et al. (*9*) have shown that asbestos fiber processing operations do generate fibrous aerosols with relatively high charge levels, and that these charge levels are sufficient to cause an enhancement of fiber deposition in the lungs. Such an enhancement of fiber deposition for chrysotile asbestos in rats exposed by inhalation was demonstrated by Davis et al. (*10*).

Interception increases with fiber length. The greater the length, the more likely that the position of a fiber end will cause it to touch a surface that the center of mass would have missed.

Diffusional displacement results from collisions between air molecules and airborne fibers. For compact particles, diffusion becomes an important deposition mechanism for diameters smaller than about 0.5 μm. Fibers of similar diameter would be more massive and therefore be displaced less by a single molecular impact. A long fiber may have nearly simultaneous impacts from several gas molecules and their random trajectories may tend to damp the net displacement. On the other hand, a single collision near a fiber end may rotate the fiber sufficiently to alter its interception probability. At the present time, the role of diffusion in fiber deposition is poorly understood. Gentry et al. (*11*) measured the diffusion coefficients of chrysotile and crocidolite asbestos fibers and found good agreement with theoretical predictions for chrysotile (0.4 μm mean diameter), but poor agreement with the more rodlike crocidolite (0.3 μm mean diameter).

Air is inhaled either through the nose or mouth, or partially through each. The air that enters through the nose has the more tortuous path. Fibers can be removed from the airstream by impaction at the anterior nares. Further downstream, impaction and interception can take place on the nasal hairs, and at epithelial surfaces distal to further sharp changes in airflow direction. Some fibers may deposit by sedimentation in the larger nasal airways and nasopharynx, where the residence times may be sufficiently long for the fiber to descend to a surface.

The conductive airway region of the human lung consists of a series of bifurcating airways. The trachea is the only airway segment with a length-to-diameter ratio much greater than three. Single symmetrical fibers suspended in a laminar flow stream should tend to become aligned with the flow axis as they move through a lung airway. On the other hand, fiber agglomerates or nonfibrous particles would have more random orientations that would depend on their distributions of masses and drag forces. A fiber whose flow orientation differs from axial alignment would have an enhanced probability of deposition by interception.

A fiber's alignment is radically altered as it enters a daughter airway, and this loss of alignment with the flow at the entry of the daughter tube contributes to its deposition by interception at or near the carinal edge. To the extent that a fiber is entrained in the secondary flow streams that form at bifurcations, its deposition probability by interception should be further enhanced.

Sussman (*12*) performed an experimental study of fiber deposition within the larger tracheobronchial airways of the human lung using replicate hollow airway casts. For crocidolite fibers with diameters primarily in the 0.5 to 0.8 μm range, interception increased total deposition, with the effect increasing with fiber length, especially for fibers > 10 μm in length. The effect was most pronounced at a high flow rate, i.e., 60 L/min. At a lower flow rate, i.e., 15 L/min, the effect was less pronounced, although still significant. This is consistent with greater axial alignment of the fibers during laminar flow within the airway.

Morgan and Holmes (*13*) and Morgan et al. (*14*) exposed rats for several hours by inhalation (nose only) to glass fibers 1.5 μm in diameter, and 5, 10, 30, or 60 μm long. For fibers longer than 10 μm, essentially all of the fibers were deposited, mostly in the head. These results, together with the results of their earlier studies on asbestos fibers, indicate that penetrability of airborne fibers into the rat lung drops sharply with aerodynamic diameter above 2 μm. The results reported by Morgan and Holmes are also very important in terms of their experimental verification that increasing fiber length increases the proportion of the lung deposition that takes place in the tracheobronchial airways.

Sussman (*12*) found that the deposition patterns of fibers in the larger lung airways are similar to those for particles of more compact shapes. In other words, the added deposition due to interception increased the deposition efficiencies without changing the pattern of deposition. Most of the studies on particle deposition patterns and efficiencies in hollow bronchial airway casts of the larynx and the larger conductive airways of the human bronchial tree have been focused on deposition during constant flow inspirations. A significant body of data has also been generated at NYU for deposition during cyclic inspiratory flows. For these tests (*15,16*) we used a variable orifice mechanical larynx model (*17*) at the inlet, while fixed orifice laryngeal models were

used in the constant flow test. In one series of tests, we used two replicate casts in tandem. The corresponding terminal endings were connected with rubber tubing. Deposition in the downstream cast was analyzed to determine the deposition pattern and efficiencies during expiratory flow (*18*).

Concern about sites of enhanced surface deposition density is stimulated by the observation that the larger bronchial airway bifurcations, which are favored sites for deposition, are also the sites most frequently reported as primary sites for bronchial cancer (*19*). Deposition patterns within the nonciliated airways distal to the terminal bronchioles may also be quite nonuniform. Brody et al. (*20*) studied the deposition of chrysotile asbestos in lung peripheral airways of rats exposed for 1 hr to 4.3 mg/m^3 of respirable chrysotile. The animals were killed in groups of 3 at 0, 5, and 24 hr and at 4 and 8 days after the end of the exposure. The pattern of retention on the epithelial surfaces was examined by scanning electron microscopy of lung sections cut to reveal terminal bronchiolar surfaces and adjacent airspaces. The rat does not have recognizable respiratory bronchioles, and the airways distal to the terminal bronchioles are the alveolar ducts. In rats killed immediately after exposure, asbestos fibers were rarely seen in alveolar spaces or on alveolar duct surfaces, except at alveolar duct bifurcations. There were relatively high concentrations on bifurcations nearest the terminal bronchioles, and lesser concentrations on more distal duct bifurcations. In rats killed at 5 hr, the patterns were similar, but the concentrations were reduced. Subsequent studies have shown that crocidolite asbestos (*21*), Kevlar aramid synthetic fibers (*22*), and particles of more compact shape (*23*) also deposit in similar patterns, and that the deposition patterns seen in the rat also occur in mice, hamsters, and guinea pigs (*24*).

The sudden enlargement in airpath cross-section at the junction of the terminal bronchiole and alveolar duct may play a role in the relatively high deposition efficiency at the first alveolar duct bifurcation. Little has previously been known about the flow profiles in this region of the lung. However, Briant (*25*) has shown that a net axial core flow in a distal direction and a corresponding net annular flow in a proximal direction take place during steady state cyclic flow in tracheobronchial airways, and that this could account for such concentrated deposition on the bifurcations of distal lung airways.

Fiber Retention, Dissolution, and Translocation

The fate of fibers deposited on surfaces within the lungs depends on both the sites of deposition and the characteristics of the fibers. Within the first day, most fibers deposited on the tracheobronchial airways are carried proximally on the surface of the mucus to the larynx, to be swallowed and passed into the gastrointestinal tract. The residence time for fibers on the surface of the tracheobronchial region is too short for any significant change in the size or composition of the fibers to take place.

Fibers deposited in the nonciliated airspaces beyond the terminal bronchioles are more slowly cleared from their deposition sites by a variety of mechanisms and pathways. These can be classified into two broad categories, i.e., translocation and disintegration.

Translocation refers to the movement of the intact fiber along the epithelial surface: to dust foci at the respiratory bronchioles; onto the ciliated epithelium at the terminal bronchioles; or into and through the epithelium, with subsequent migration to interstitial storage sites or along lymphatic drainage pathways. Translocation of either type may occur after ingestion of the fibers by alveolar macrophages if the fibers are short enough to be fully ingested by the macrophages. There may also be translocation via movement of bare fibers. Holt (*26*) proposed that fibers phagocytosed by alveolar macrophages are carried by them toward the lung periphery by passing through alveolar walls and that some of these cells aggregate in alveoli near larger bronchioles and then penetrate the bronchiolar wall. Once in the bronchiolar lumen, they can be cleared by mucociliary transport.

Disintegration refers to a number of processes, including the subdivision of the fibers into shorter segments, partial dissolution of components of the matrix creating a more porous fiber of relatively unchanged external size, or surface etching of the fibers creating a change in the external dimensions of the fibers.

For MMMF, fiber breakup is virtually all by length. The breakdown into smaller diameter fibrils which is characteristic of asbestos fibers is seldom seen. For MMMF, the relative importance of breakage into length segments, partial dissolution, and surface etching to the clearance of fibers depends upon the size and composition of the fiber.

Morgan et al. (*13,27*) studied the retention of 1.5-μm diameter glass fibers administered to rat lungs by intratracheal instillation. Retention at 1 year for 5-μm long fibers was 10%, while for 10-μm long fibers it was 20%. For the fibers which were 30 or 60 μm long, there was no measurable clearance during the first 9 months. Further retention measurements were not made for these long fibers because of evidence that they were disintegrating and dissolving. This macrophage-mediated mechanical clearance is less effective for 10-μm fibers than for 5-μm fibers, and ineffective for fibers of 30 μm length and longer. As confirmation, Morgan and Holmes (*13*) cited work of Timbrell on the dimensions of anthophyllite fibers in the lungs of Finnish workers which suggests that the critical fiber length for mechanical clearance from the lungs is approximately 17 μm.

Morgan et al. (*13,27*) found that the solubility of MMMF in rat lungs *in vivo* was dependent on both size and composition. The results were based on the sizes of fibers recovered from rats' lungs at various times following the inhalation exposures. For the glass fibers,

there was much less dissolution of the 5 and 10 μm fibers than of the 30 and 60 μm fibers. The dissolution of the long 1.5 μm diameter fibers was very nonuniform. Some were little changed in dimension, while others were reduced in diameter to 0.2 μm. On the other hand, for rockwool fibers > 20 μm in length, there was no observable change in fiber dimensions after 6 months. Morgan and Holmes (*13*) attributed the dependency of dissolution on fiber length to the differences in intra- and extracellular pH. The shorter fibers within macrophages are exposed to a pH of 7.2, while those outside were exposed to the extracellular pH of 7.4.

Dissolution of glass fibers in rat lungs *in vivo* was also observed by Johnson et al. (*28*), who exposed rats to MMMF aerosols at 10 mg/m^3 for 7 hr/day, 5 days/week for 1 year as compared to the single exposure of several hours duration used by Morgan and Holmes. The percentage of glass fibers with diameters less than 0.3 μm which were recovered from the lungs was consistently less than that in the original fiber suspension, and the reduction was more marked in the animals that were sacrificed following a period of recovery from the exposures than from those sacrificed at the end of the exposure. Furthermore, morphological examination of the fiber surfaces revealed an etching of the surface manifest as irregularities in outline, loss of electron density, and the appearance of pits along their edges. The degree of etching increased with residence times in the lungs. Glasswool with and without resin was also etched, but to a lesser extent, while the etching of the rockwool fibers was considerably less.

Bellmann et al. (*29*) instilled suspensions of UICC crocidolite, UICC chrysotile A, and glass fibers in rat lungs, and examined the residual fibers after 1 day and 1, 6, 12, and 15 months. They reported that crocidolite fibers longer than 5 μm did not decrease in number for over 1 year. The number of chrysotile fibers > 5 μm doubled, probably due to longitudinal splitting, while the number of > 5 μm glass fibers was reduced with a halftime of 55 days, due to dissolution. All fibers < 5 μm in length were cleared with halftimes of 100 to 150 days. When the crocidolite fibers were pretreated in acid there was no change in retention. On the other hand, acid-treated chrysotile and glass fibers had much more rapid clearance, with halftimes of 2 and 14 days, respectively.

In a 2-year follow-up study, Bellmann et al. (*30*) reported the persistence of some MMMF, crocidolite, and chrysotile in the rat lung after intratracheal instillation. Experiments were based on the assumption that thin, long and durable fibers are of special importance for the carcinogenic potency of these types of substances. Parameters measured included number of fibers, diameter and length distribution of fibers retained in lung ash and leaching of various elements from fibers longer than 5 μm. For a special type of glass microfiber and for ceramic wool, which both had a low alkaline earth content, the halftimes of lung clearance were at a level similar to that of crocidolite. For another type of glass microfiber with a high alkaline earth content and a median diameter of about 0.1 μm, a very low halftime was reported. The glass and rock wools studied, which were thicker than the other fibers, had a medium halftime.

In the inhalation study of Brody et al. (*20*) with chrysotile, their examination of tissues by transmission electron microscopy revealed that fibers deposited on the bifurcations of the alveolar ducts were taken up, at least partially, by Type I epithelial cells during the 1 hr inhalation exposure. In the 5 hr period after exposure, significant amounts were cleared from the surfaces, and there was further uptake by both Type I cells and alveolar macrophages. Within 24 hr after the exposure, there was an influx of macrophages to the alveolar duct bifurcations. The observations provide a basis for fiber penetration of the surface epithelium which does not hypothesize movement within macrophages.

Bernstein et al. (*31*) and Hammad (*32*) also found evidence of substantial *in vivo* dissolution. LeBouffant et al. (*33*) used X-ray analysis on individual fibers recovered from lung tissue to show the exchange of cations between the fibers and the tissues. For example, the fibers can lose Ca and gain K. Insight on the solubility of fibers *in vivo* has also been obtained from *in vitro* solubility tests, as indicated in my recent MMMF review (*6*).

Discussion

There has been a significant advance in our knowledge about the deposition and elimination of fibers in recent years, as well as some new knowledge about exposure-response in controlled animal inhalation studies; some further concern about lung cancer among heavily exposed workers in the MMMF industry; and some new insight into the critical fiber properties affecting disease pathogenesis.

MMMF differ from asbestos fibers in several critical ways, which tend to result in less lung deposition, and in the more rapid elimination of those fibers that do deposit in the lungs. One is in diameter distribution. Except for glass microfiber, MMMF tend to have relatively small mass fractions in diameters small enough to penetrate through the upper respiratory tract. Asbestos, on the other hand, usually contains more respirable fiber. Furthermore, once deposited, the asbestos fibers may split into a greater number of long thin fibers within the lungs. MMMF rarely split, but are more likely to break into shorter length segments.

There are also differences in solubility among the fibers that affect their toxic potential, both among the asbestos types and the MMMFs. Conventional glass fibers appear to dissolve much more rapidly than other MMMFs and asbestos. Dissolution of glass fibers takes place both by surface attack and by leaching within the structure. The diameters are reduced and the structure is weakened, favoring break up into shorter segments. Since the smallest diameter fibers have the greatest surface-to-volume ratio, they dissolve most rapidly. Thus, the relatively small fraction of the airborne glass fibers with diameters small enough to penetrate into

the lungs are the most rapidly dissolved within the lungs.

The more durable and less soluble MMMF, i.e., slag- and rockwool, some specialty glasses, and ceramic fibers, require a higher degree of concern because of their longer retention within the lungs. *In vitro* studies and studies of dissolution in simulated lung fluids can be very useful in preliminary evaluations of the toxic potential of the various MMMFs (*6*). On the other hand, the dissolution of MMMF *in vivo* depends upon many additional factors which cannot readily be simulated in model systems. For example, the differences in *in vivo* solubility of long and short fibers noted by Morgan and Holmes (*13*) were attributed to small difference in intracellular and extracellular pH. The mechanical stress on fibers *in vivo* may also contribute to their disintegration, and cannot readily be simulated in model systems. Thus, hazard evaluations of specialty product MMMFs, made for limited and specific applications, should continue to be subjected to detailed *in vivo* studies in which animals are exposed to appropriate sizes and concentrations of the fibers of interest.

Conclusions and Research Recommendations

My earlier review demonstrated the critical role of fiber dimensions on the pathogenesis of the chronic diseases associated with inhalation exposures to asbestos and other natural mineral fibers (*1*). In summary, short fibers were shown to be essentially nuisance dust. Very thin fibers (i.e., <0.1 μm diameter) can cause mesothelioma, while thicker fibers can cause fibrosis and lung cancer. This paper has examined the underlying roles that the physicochemical properties of mineral fibers play in modifying the pathogenic responses associated with inhaled fibers. The critical role of fiber dimensions is confirmed by the evidence that those MMMFs in the right size range and having sufficient durability within the body can also cause lung cancer in exposed workers (*5*). Fibers, such as conventional fibrous glass, with lesser fractions having the critical dimensions for pathogenic response and lesser durability within the body, have not been associated with excess cancer in workers (*5*).

Artificial *in vivo* tests in animals that enhance the yields of fibrosis and mesotheliomas provide further evidence of the critical roles of fiber dimensions and durability on fiber toxicity. Virtually all fibrous minerals containing long fibers (i.e., > 10 μm in length) produce lung fibrosis following intratracheal instillation, with the potency ranging from very high for asbestos to very low for conventional fibrous glass. Similar potency rankings apply to mesothelioma yields following intrapleural injections of fiber suspensions or implantations of fiber mats. These potency rankings indicate that the elemental compositions of the fibers play little, if any, role in fiber toxicity, except insofar as they affect the fiber durability in cells and lung fluids.

It appears that fibers, as physical entities, stimulate cellular responses and enzyme secretions at critical target sites, leading to alterations in cell functions, differentiation patterns, numbers, and distributions. When the fibers are sufficiently durable in the lung, or at the pleura after translocation, the stimulation can continue for a sufficient time to produce chronic structural alteration and disease. Kuschner (*34*) has suggested that the strikingly lesser tendency of MMMF to induce malignant tumors when introduced into the lung experimentally may be determined by its lesser degree of fibrogenicity, fibrosis being a precondition for the development of malignant tumors induced by fibers; also that fibrogenicity, in turn, is determined by fiber dimension, by physicochemical characteristics of fiber and by durability. Inhalation of MMMF in man may not produce the scarred lung and pleura that must precede the development of carcinoma and mesothelioma. Clearly, Kuschner raises a research question which can and should be addressed, i.e., fibrosis as necessary precondition for tumorigenicity.

Pott (*35*) has stated that: "A fiber has to be regarded as a physical carcinogen that works by its elongated shape. Clearly, a fiber which is both durable and persistent should have a stronger effect than a non-durable or non-persistent one. In this context some questions have to be put to the cell biologist: How long do fibers have to stay in the bronchial wall or serosa tissue in order to cause an alteration that can lead to the development of a tumor? Is persistence for just one cell division phase in principle sufficient for a transforming effect? Or does the (unknown) mechanism need a longer period? Is the minimum persistence period for a transforming effect related to the cell division period of the host species? Does a longer persistence time lead to a proportionately greater effect by affecting more cell generations, which would result in a higher tumor incidence and/or shorter latency period?"

These are well-stated research questions for cell biologists. Pott (*35*) also formulated an important research question that requires whole animal toxicology and extrapolation modeling, i.e., How long must fibers persist in the human body in order to induce the biological alterations that can lead to bronchial carcinomas or mesotheliomas without the further presence of fibers? The shortest necessary period of persistence can be seen as a kind of threshold value. Based upon his knowledge of minimal latency in asbestos workers, Pott constructed a model for human cancer development following exposure to airborne fibers (Fig. 1).

At this point, we are able to frame the important questions concerning fiber toxicology. If this workshop can help to refine and prioritize the questions and stimulate the research sponsors to initiate and support the necessary program, it should be possible in the near future to greatly improve our abilities to *a)* define the hazards associated with specific fiber exposures by analysis for concentrations of fibers having critical dimensions in terms of toxicity, *b)* provide a rational basis for decisions to remove asbestos and/or other fibers, or

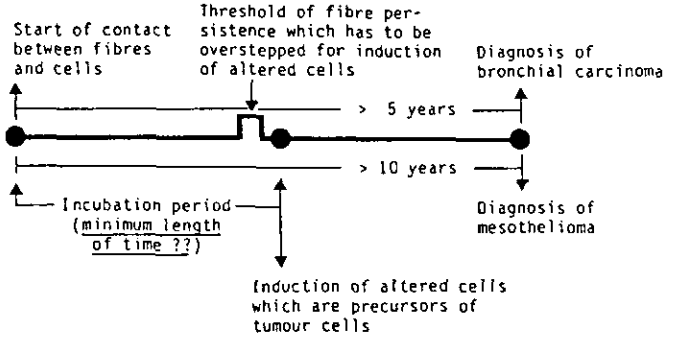

FIGURE 1. Diagram illustrating the question of the minimum length of the incubation period necessary for the induction of precursors of tumor cells.

to leave them in place, based upon their composition, fiber size distribution and physical condition, and *c)* guide the development of safe substitutes for hazardous fibers that should be removed.

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