Biopersistence of Respirable Synthetic Fibers and Minerals: The Point of View of the Epidemiologist

Paolo Boffetta

International Agency for Research on Cancer, Lyon, France

Biopersistence of fibers and minerals in human respiratory tissues is an important aspect of the toxicity of these agents. However, few data are available from human studies. Although a number of studies have measured the lung burden of asbestos and other minerals in exposed humans, few presented information relevant to biopersistence of these agents. The studies analyzing asbestos lung burden in workers at different intervals following cessation of exposure suggest a linear decrease in concentration over time, that is independent of duration of exposure. However, the available evidence on asbestos is too sparse to allow a firm conclusion; almost no data are available on other minerals. — Environ Health Perspect 102(Suppl 5):11–13 (1994)

Key words: asbestos, biopersistence, epidemiology, synthetic fibers, minerals

Introduction

Biopersistence of fibers and minerals in human respiratory tissues is an important aspect of the toxicity of these agents.

The causal pathway leading to chronic damage caused by an external agent can be viewed as a model including six steps (Figure 1) (1). In epidemiologic studies of the fibrogenic or carcinogenic action of inorganic agents, a qualitative or semiquantitative estimate of external exposure is usually the only information available on dose. Furthermore, little information is available on early biologic effects or altered structure functions, and the pathway leading to chronic disease from external exposure is not known. Biopersistence is among the factors that influence the biologically effective dose, which is defined as the amount and type of inhaled fibers or minerals interacting with the appropriate biologic targets. A valid estimate of the biologically effective dose would greatly assist the interpretation of results of epidemiologic studies, especially in studies dealing with low exposures and doses.

Biopersistence of Fibers and Minerals in Humans

Although a number of investigators have analyzed the content of fibers (mainly asbestos) and other minerals in human respiratory tissues (mainly the lung), these studies are of limited value to elucidate the processes of retention, dissolution, and translocation of the inhaled material. From recent reviews on asbestos (2,3), it can be concluded that the asbestos content of lung tissue is higher in asbestosis and lung cancer patients than in patients with pleural mesothelioma or pleural plaques (2). However, differences in analytic techniques, and in the physical characteristics of fibers, make the comparison of results between studies somewhat problematic.

No study has so far specifically addressed the issue of persistence of fibers or minerals in the human lung. The difficulties in carrying out such a study are briefly reviewed below. However, a few studies have analyzed asbestos content in lungs of miners, textile and asbestos cement workers at various intervals after cessation of exposure. Such investigations offer some information on the biopersistence of asbestos fibers in human lungs.

Sebastien et al. measured fiber content in 161 lung tissue samples of asbestos textile workers from South Carolina, and asbestos miners and millers from Quebec (4). The main purpose of the study was to explain the higher risk of respiratory cancer in textile workers than in miners, both exposed to chrysotile from the same kind of fiber source. The authors present concentrations of chrysotile and tremolite according to duration of employment and time since cessation of employment. Although the number of samples in some duration cessation cells is small, a decrease in concentration of both types of fiber with time since cessation of employment is suggested among both textile workers and miners exposed for 200 months or more; results for workers exposed for a shorter period are less easily interpretable (Figure 2).

Concentration of asbestos fibers according to time since first exposure (latency), duration of exposure, and time since cessation of exposure were also presented by Pooley (5), who analyzed lung tissue of 20 cases of asbestosis among Canadian chrysotile miners, 16 of whom had a detectable level of fibers (5); by Gylseth, Mowe, and Wannag, who presented results based on four mesothelioma and four lung cancer cases among workers in a Norwegian asbestos cement plant mainly exposed to chrysotile (6); and by Dodson et al., who analyzed lung tissue samples from 12 workers of a Texas amosite plant, six of whom were employed for not more than 3 months (7).

Results of these studies according to duration of exposure and time since cessation of exposure are presented in Figure 1. The duration of exposure and the time since cessation of exposure are two independent determinants of the concentration of asbestos fibers in the lung. The concentration of fibers remains high for many years after cessation of exposure (8,9), but decreases with time and is lower in newer exposure groups. The concentration of fibers is also dependent on the type of fiber. The concentration of chrysotile is higher than that of asbestiform amphiboles. The concentration of fibers in the lung also depends on the size of the fiber. The concentration of short fibers is lower than that of long fibers.

Figure 1. Model of pathway between exposure and disease.
tion of exposure are reported in Figures 3 and 4. In addition to univariate linear regression analysis, a multivariate analysis was carried out on the original data to assess the combined effect of duration of exposure and time since cessation of exposure. Results of the regression analyses are shown in Table 1.

These studies consistently show a correlation between lung fiber concentration and duration of exposure. The first two studies also show a negative correlation with time since cessation of exposure, whereas Dodson et al. did not show any correlation between cessation of exposure and lung fiber concentration. Differences in the results may be explained by the different type of fibers, the different exposure pattern (cumulative dose and dose rate) experienced by the study subjects, the different analytic methods used for fiber determination, and the statistical imprecision due to the small sample size.

In a study of bronchoalveolar lavage measurements of lung dust levels in granite workers from Vermont, no effect of retirement was shown, since bronchoalveolar lavage materials still contained large amounts of minerals even a decade after exposure ceased; however, detailed data were not shown (8).

At least in the case of asbestos, the sparse epidemiologic evidence points toward a reduction in fiber lung content after cessation of exposure. It is not possible to make a precise estimate of the disappearance rate from available data, nor to distinguish between clearance mechanisms with very different biologic significance, such as dissolution or migration to the pleura. However, the fact that minerals and fibers persist in the respiratory tract after cessation of exposure, and that, at least for asbestos, they may decrease in concentration over time, has profound implications in the interpretation of epidemiologic studies. Cumulative exposure may not be an appropriate indicator of biologically effective dose, and variables such as dose rate and time since cessation of exposure should be taken into account in the analyses.

Identification of Mechanisms of Carcinogenicity

Peto et al. observed that mesothelioma death rates in asbestos workers appear to be proportional to the third or fourth power of time since first exposure (9). The fact that age at first exposure had little influence on risk supports the hypothesis of an effect of asbestos on an early step of the carcinogenic process (10). In contrast, asbestos seems to act as a late-stage carcinogen on the lung (9). Clearly, persistence of fibers in the lung and migration to the pleura complicate the interpretation of the epidemiologic results with respect to mechanisms of carcinogenicity. In particular, a long retention time may cause an overestimation of the carcinogenic effect per dose unit. Similar models are not available for minerals other than asbestos.
Options for Future Research

Ideally, an epidemiologic study aimed at clarifying the role of biopersistence of fibers and minerals in the causation of fibrosis or cancer in humans should have, in addition to the measurement of the health outcome, a physicochemical determination of the inhaled materials, a valid measurement of external dose and dose rate (average and peak level of exposure), and repeated measurements of the agents in the target tissues. The latter requirement could be only exceptionally fulfilled, (as for example, in a worker who underwent a lobectomy a few years before dying). Therefore, human studies on mineral lung burden will continue to be based on measurements carried out at surgery or necropsy, irrespective of the exposure history of subjects.

Human research on biopersistence can be improved in a number of aspects. First, the exposure history of subjects can be carefully characterized with respect to the type of material, average exposure in different periods, time since beginning and cessation of exposure, and possibility for exposure after cessation of employment in the industry under study. Furthermore, existing studies on asbestos lung burden can be combined and reanalyzed, making it possible to clarify the role of fiber type, latency, duration of exposure and time since cessation of exposure. Existing cohort studies of asbestos-exposed workers can be reanalyzed with different assumptions on persistence of fibers in the lung, leading to different estimates of cumulative exposure. Finally, human studies on minerals other than asbestos are clearly needed.

Among the questions that experimental studies may address that are of primary value for the interpretation of epidemiologic studies are the effect of biopersistence of minerals after intratracheal or intracavity administration as compared to inhalation, the effect of similar cumulative exposure at different dose rates, and the effects of different types of asbestos fibers and of minerals other than asbestos.

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