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Discussion: Dose-Response Relationships for Asbestos-Related Disease;
Implications for Hygiene Standards

DOSE-RESPONSE RELATIONSHIPS FOR
ASBESTOS-RELATED DISEASE:
IMPLICATIONS FOR HYGIENE STANDARDS
PART I. MORBIDITY

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It is well established that exposure to asbestos dust results in asbestosis, lung carcinoma, or mesothelioma in a proportion of those exposed and, as far as is known, the complete prevention of disease due to exposure to asbestos dust could only be achieved if the exposure level was reduced to zero. Unfortunately, it is not possible to attain this ideal, and therefore it is necessary to reduce exposure levels to as low as possible. There are several methods that may contribute to this end; they include the substitution of other materials for asbestos, the encouragement of better work practices, and the decision on some upper limit to the amount of dust so that exposure is limited, even in the most dusty workplaces.

Because the purpose of a hygiene standard is to prevent disease, information is required on the dose-response relationship. However, since the effects on health are not observed until many years after first exposure, the evidence on the health risk is necessarily mainly confined to groups first exposed 25 or more years ago. The dust levels experienced by groups currently exposed are less than those that occurred 25 or more years ago, the reduction having taken place because of a growing awareness of the health hazards.

There are, however, few data on the dust levels that occurred until relatively recently, and even those that are available have usually been obtained by use of sampling techniques different from those now employed. Consequently, there are few studies that attempt to relate measured dust concentrations to the observed health effects. It is only from studies of this type that it is possible to assess the likely health effects of exposure at the current hygiene standards or at levels currently in existence, which in many cases are well below the hygiene standards, or at hygiene standards that may become effective in the future.

In this paper, data on the morbidity in an asbestos textile factory in the north of England are reviewed. This study is an extension of the study that was included in the British Occupational Hygiene Society's report of 1968.¹ The early study had several limitations, most of which were recognized at the time, and the present study is an improvement in four ways: (i) the study is not restricted to current workers; (ii) the

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health effects have been assessed by use of the combined efforts of four physicians, three of whom were from outside the factory; (iii) less reliance is placed on estimated dust levels before 1951, when routine dust sampling was introduced; (iv) allowance is made for development of disease after the end of exposure by considering other measures of dust exposure besides cumulative dose.

The methods and results have been described in more detail by Berry *et al.*,² and a mortality study of the same factory has been reported by Peto *et al.*³

SUBJECTS AND METHODS

Only men who by the end of 1972 had worked for more than 10 years in scheduled areas of the factory since 1933 were included, except that men who had left the factory

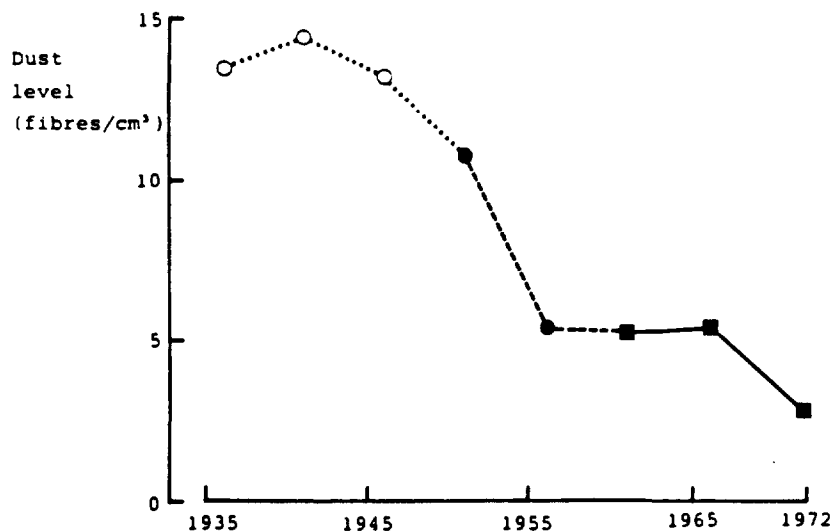


FIGURE 1. Average dust levels in asbestos textile factory, 1936-72. The levels before 1951 are probably underestimates. O, Estimated; ●, measured with thermal precipitator and converted to fiber counts; ■, measured fiber counts.

before June 30, 1966, the date that the group was defined in the original study,¹ were not included. There were 392 men who satisfied these conditions, and 197 of them were first employed in 1951 or later.

Fiber counts had been made regularly at static sampling points since 1961. From 1951 to 1960, thermal precipitator particle counts were made, and these counts have been converted to fiber counts by use of factors that were calculated on the basis of observations made in 1960 and 1961 at corresponding sites by the two methods. For 1933-50, no measured dust concentrations were available, and the figures used are based on the assumption that the levels in 1933 were 1.5 times those that existed in 1950; these figures are probably underestimates.¹

The mean fiber counts are shown in FIGURE 1. There has been a considerable improvement in conditions since 1945, but even so it was not until after 1966 that

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more than half of the men working in production areas were exposed to an average concentration of less than 5 fibers/cm³. In 1966, approximately one of every four men was exposed to a level of less than 2 fibers/cm³.

A detailed job history was obtained for each man in the morbidity study, and for each job description dust levels were calculated by taking the average of the levels measured at the dust sampling locations where the job was carried out. Thus, an estimate was obtained for each man's exposure in each year during his employment in the factory.

When the detailed job histories were being compiled, it proved impossible to produce an adequate history for one man, and it was found that 12 men had worked for several years in a subsidiary factory, where they were employed in the preliminary treatment of crude asbestos. Dust conditions at this factory were unknown, and these men have therefore been excluded.

Most of the asbestos processed in the factory since 1933 has been chrysotile. However, some crocidolite was also processed up to 1968, and it has not been possible to divide the study population into those exposed and those not exposed to crocidolite.

Those men in the morbidity study who had left the factory before the end of 1972 were invited back for a medical examination, and 60% accepted the invitation.

Each man's records in the factory's medical department were examined, and a note was made of whether the factory medical officer had heard basal crepitations (rales) that did not clear on coughing. The most recent chest radiograph was assessed by four readers independently, and the most recent lung function data were extracted. A note was also made of whether the factory medical officer had thought that the man had possible asbestosis. This diagnosis was made if the medical officer thought a man was developing symptoms or signs of early asbestosis, in which case he would advise the man to move to a less dusty job in the factory. The medical officer based his advice on crepitations, radiologic changes, a falling gas transfer, and restrictive changes in lung volumes or ventilatory capacity. An independent clinician compared the factory medical officer's opinion on whether each man had possible asbestosis with the medical information given above and had doubts about the diagnosis, or lack of diagnosis, for several men. The complete medical files of these men were examined by the factory medical officer and clinician together, and agreed diagnoses were reached.

MEASURES OF EXPOSURE

When a man has been exposed to asbestos at varying concentrations over a period of many years, the problem involves determining what measure of exposure may best be regarded as a measure of risk. The simplest measure of total exposure, and the one usually used, is the cumulative exposure, which may be defined as the average concentration experienced in each year summed over the whole period of exposure. This measure attaches the same weight to exposure a long time ago as to recent exposure and also does not alter after the end of exposure. These properties are unrealistic for asbestosis, which is dependent more on early exposure than on recent exposure and which, as shown by Becklake,¹⁴ may develop after exposure has ended. A measure that does not suffer from these disadvantages is obtained if the average concentrations in each year of exposure are weighted by the time that has elapsed since each year's exposure.⁴⁻⁶ Thus, exposure 25 years ago is considered five times as important as exposure five years ago. In addition, since the elapsed time continues to increase after exposure has ended, the measure also continues to increase in the absence of exposure.

One way of looking at this measure is to regard the weighting factor as the time

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that the dust would have been in the lungs if there were no elimination. If it is postulated that elimination of dust does occur, the measure may be generalized.² Suppose that, over the long term, dust is eliminated from the lungs at a rate proportional to the amount in the lungs, that is, there is exponential elimination, the rate of elimination, then, may be expressed as the time for half of the dust to be eliminated. Suppose further that each component of dust deposited in the lungs contributes to the risk of disease for the time it remains in the lungs. A family of measures of exposure is then produced; the family is indexed by the half-life of the exponential elimination and contains, as extreme cases, the cumulative exposure (half-life zero) and the cumulative exposure weighted by the elapsed time (half-life infinity, or no elimination).

RESULTS

In 1966, crepitations were recorded in 6% of the men¹ (TABLE 1). The most striking difference observed in the present study was that crepitations were heard in 22% of the men. In part this increase is due to differences in the methodology. In 1966, only current workers were included, but the present study also included men who had left the factory; crepitations were heard in 17% of workers still employed at the end of 1972 and in 29% of those who had left. Part of the increase may be a difference between observers, since the factory medical officer retired and was replaced in 1967. The third reason for the increase in the proportion of men with crepitations is the longer follow-up.

There were 58 cases of possible asbestosis, and 47 of these cases had occurred since the middle of 1966. In FIGURE 2, the cases that occurred since 1966 are shown as incidences per year by dividing the number of cases by the man-years of follow-up. These incidences have been plotted against the cumulative exposure, evaluated up to the middle of 1966, and the total group has been divided into two, those men first employed at the factory before 1951 and those first employed after 1950. The data are compatible with a linear relationship through the origin, with no statistically significant difference between the two groups. The lack of disagreement between the two groups may be fortuitous; the cumulative exposure of the group first employed before 1951 has probably been underestimated, but failure to allow for elimination will, to some extent, have compensated for this difficulty. The data on possible asbestosis will be explored in more detail later.

Men First Employed after 1950

Dust measurements were not made before 1951, and therefore the cumulative exposures given for men starting earlier depend on the assumptions made on the levels

TABLE 1
PREVALENCE OF CREPITATIONS

1966 study		
Employed 30 June 1966	16/290	6%
Present study		
Total	82/379	22%
Employed December 31, 1972	42/241	17%
Left before December 31, 1972	40/138	29%

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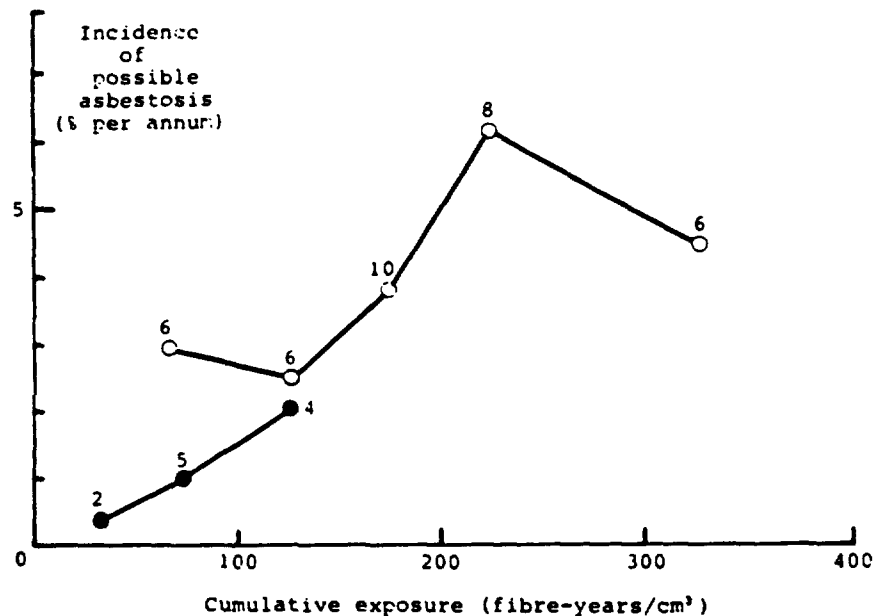


FIGURE 2. Incidence of cases of possible asbestosis since 1966 in relation to cumulative exposure up to 1966. The number of cases is given by each point. The cumulative doses of those first employed before 1951 (○) include estimated dust concentrations and are probably underestimated. ●, First employed after 1950.

that occurred between 1933 and 1950. In addition, since men who left before the middle of 1966 were not included in the study, there is a bias, which is largest in the group who started employment before 1951. Although there is also a bias for this reason in the group who started after 1950, this bias is small.² Therefore, in further discussion of the data, attention will be restricted to those first employed after 1950. Although this restriction does have the disadvantage of reducing the amount of data, this reduction occurs mainly by excluding those with higher cumulative exposures, and therefore those with least relevance to the current dust hygiene standards.

The lung function measurements have been expressed as percentages of predicted values after allowing for age and height. The forced expiratory volume was associated significantly with the cumulative exposure, with a reduction of 12.1% (standard error 3.9%) per 100 fiber-years/cm³. The same was true for the forced vital capacity ($10.6 \pm 3.5\%$), while the reduction in transfer factor, $6.9 \pm 4.6\%$ per 100 fiber-years/cm³, was not statistically significant but large enough to be important.

The chest radiographs had an average profusion of small irregular opacities of category 0/0 in 122 of 197 men (62%), category 0/1 in 46 men (23%), 1/0 in 18 men (9%), 1/1 in six men (3%), and for five men (3%), the category was 1/2 or above. There were 34 men for whom two or more of the four readers recorded pleural thickening, and for nine of these men, the thickening was bilateral; 13 of the unilateral and seven of the bilateral cases also had small irregular opacities of category 0/1 or more.

Possible Asbestosis and Measures of Exposure

Dose-response relationships were fitted to the prevalence of possible asbestosis and several members of the family of exposure measures discussed earlier. It was found that the data were insufficient to estimate the rate of elimination of dust from the lungs; any member of the family of exposure measures in which it took three or more years for half of the dust to be eliminated was satisfactory.

The family of exposure measures is illustrated in FIGURE 3, in which a group of men exposed to 5 fibers/cm³ for 20 years has been considered. The estimated prevalence of possible asbestosis during this period, and also in the 20 years after exposure ended, is shown for several exposure measures. The prevalence at the end of exposure is almost independent of the measure of exposure due to the fact that 20

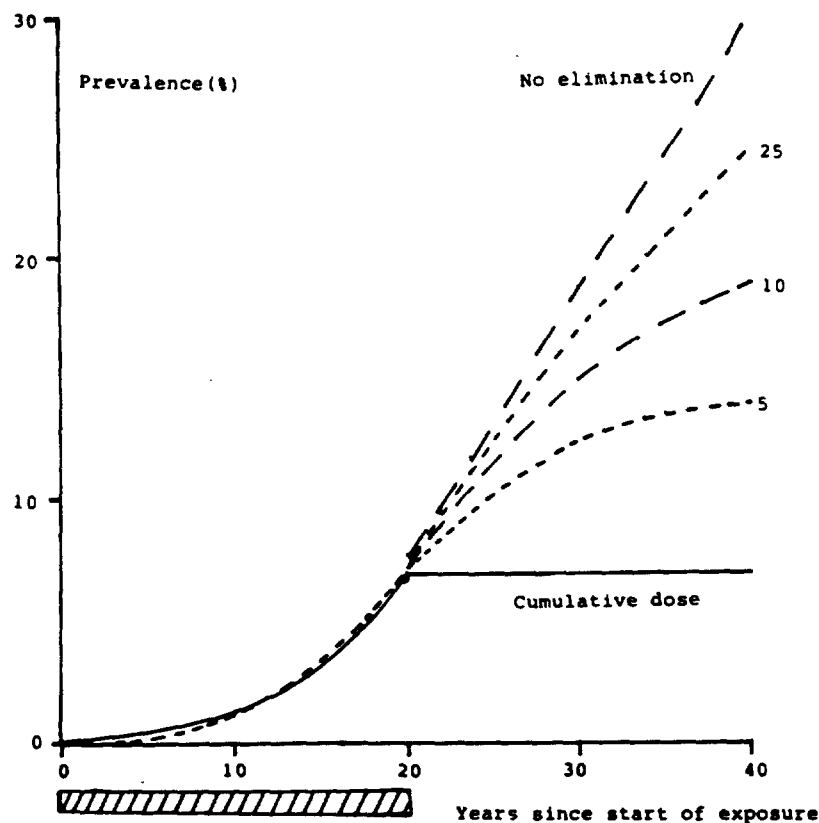


FIGURE 3. Estimated prevalence of possible asbestosis during, and for 20 years after the end of, 20 years of continuous exposure to 5 fibers/cm³. The relationships are shown for five members of the family of exposure measures discussed in the text: cumulative exposure, cumulative exposure weighted by time since exposure (no elimination), and cumulative exposure weighted by residence time of dust in the lungs, where exponential elimination is assumed to take place with half-lives of 5, 10, or 25 years.

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TABLE 2
ESTIMATED PREVALENCE OF POSSIBLE ASBESTOSIS AFTER CONTINUOUS EXPOSURE TO 2
FIBERS/CM³ FOR 30, 40, AND 50 YEARS

Half-life of Dust Elimination from Lungs (years)	Estimated Prevalence (%) at End of Exposure of		
	30 Years	40 Years	50 Years
0 = cumulative dose	2	4	7
5	4	7	11
10	5	9	15
25	6	12	19
∞ = no elimination	7	14	24

years' exposure to 5 fibers/cm³ is typical of the data used to estimate the relationships. In contrast, the increase in prevalence after the end of exposure differs widely because only a few data in this study relate to at most seven years after the end of exposure.

The current hygiene standard in the United Kingdom is 2 fibers/cm³, and therefore it is relevant to predict the prevalence of possible asbestosis that would occur after being exposed to this level for a working life. TABLE 2 shows the estimated prevalences after 30, 40, and 50 years' exposure. After 40 years, cumulative exposure gave a prediction of 4%, whereas the assumption that there was no elimination of dust from the lungs gave 14%. The reason for this wide range is that the predictions are all extrapolations from shorter lengths of exposure (average 16 years) at higher dust levels (average 5 fibers/cm³).

DISCUSSION

Other Employment

Most of the men in the study had been employed elsewhere before being exposed to asbestos in the factory; only 40% were first employed at the factory before the age of 30. Of the 13 men who started at the factory after 1950 and who had possible asbestosis, five had previously worked in the cotton industry. One of these five men had been a stripper and grinder for 20 years, and a recent survey in the Lancashire cotton industry has confirmed that this job has a high risk of respiratory disease.⁷ This man reached the possible asbestosis category in eight years and was the quickest occurring case. Another man had previously been a chemical worker for 20 years and was certified as suffering from asbestosis after 12 years in the factory. It is therefore probable that some of the signs observed in this study were, at least in part, attributable to other occupations.

Dust Sampling

The dust concentrations used were obtained from static sampling sites, and although they have been related to the individual men in the study as closely as possible, this process can take no account of individual work-styles. There may be considerable differences in the actual exposure of men recorded as doing the same job

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in the same area of the factory. This may explain why a dose-response relationship obtained by use of time since first exposure fitted the data just as well as did relationships obtained with the various cumulative exposure measures. If the main interest was in the effect of the measured dust levels, this would not cause much difficulty, but extrapolation to lower dust levels introduces a bias. The reason for this bias is that some men with disease would be recorded as having a lower exposure than they had received. Of course, the opposite would also occur, but the errors do not cancel out when a dose-response relationship is fitted. The effect of the errors is to produce a flatter dose-response curve, which would intersect the true dose-response curve near to the mean exposure. Thus, the health risk is exaggerated at low levels. The exposures of asbestos workers are now assessed by use of personal samplers. These samplers should provide a more accurate measure, but hygiene standards assessed on less accurate data obtained from static samples but applied by use of personal samplers would provide a greater degree of protection than would be concluded from the observed dose-response relationship.

Significance of Possible Asbestosis

Possible asbestosis is a diagnosis based on several indices, none of which is specific to asbestos exposure. Crepitations may be due to bronchiectasis, and pulmonary fibrosis may be detected on the chest radiograph in the absence of any exposure to asbestos.⁸ Therefore, the diagnosis of possible asbestosis is not necessarily a consequence of exposure to asbestos in every case. The occurrence of false positives, even if there are also false negatives, leads to an exaggeration of the health risk at low levels.

Other Studies

There are few studies that relate morbidity and dust levels. McDonald *et al.*⁹ related several indicators of morbidity with cumulative exposure in chrysotile miners and millers in Quebec. The dust levels were measured as millions of particles per cubic foot (mpcf) with the midget impinger. The main conclusion was that there was a 1% risk of acquiring clinically significant disease for an exposure between 100 and 200 mpcf-years. It was not possible to convert this exposure to fiber-years/cm³ because there was a low correlation between impinger and fiber counts.¹⁰

Weill *et al.*¹¹ reported on a morbidity study in asbestos cement manufacturing plants in New Orleans. Dust sampling was achieved with the impinger, but there was some simultaneous sampling with fiber counting. The majority of the asbestos used was chrysotile. They found little evidence of a dose-response relationship for lung function measurements or irregular small opacities below a cumulative exposure of 100 mpcf-years. They equated this exposure with 200 fiber-years/cm³. There are several possible explanations for the difference between these results and the ones reported in this paper. First, Weill *et al.*¹¹ studied only workers employed on a particular date. Second, all workers were included, and some had only started work in the industry shortly before the survey; these workers would have low cumulative exposures, but the main reason for their observation of no effect would be the short time that had elapsed since they had started exposure. Third, there may be differences in the effect of similar concentrations of asbestos in the asbestos textile and the asbestos cement industries due to differences in the size distribution of the respirable fibers.

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Hygiene Standards

The purpose of hygiene standards, defined in the broad sense to encompass work practices and not just as a single figure that limits exposure level, is to reduce exposure to asbestos to prevent the development of significant disease. There is much debate on the part that a limit to dust concentration has to contribute toward this objective. The concept of a hygiene standard is sometimes criticized as if it excluded all other measures, but this is not the case. Where the most appropriate control measure is thought to be substitution of another material for asbestos, substitution should and does occur, for example, thermal insulation. Where it is technically feasible to operate at levels well below the current standard, again, this approach is not in conflict with the standard. Similar views have been expressed by Nicholson.¹²

If significant disease is defined as either disability in life or a shortening of life or both, it is not immediately apparent whether the main indicator used in the study reported in this paper, possible asbestosis, is significant disease. However, within 3½ years of diagnosis, 50% of those with possible asbestosis were certified for compensation as suffering from asbestosis by the Pneumoconiosis Medical Panel (PMP).¹ The mortality of a group of 430 asbestotics certified by PMPs between 1956 and 1965 was reported in 1967 as two or three times that of the general male population of equivalent ages.¹³ More recent data on the prognosis after certification are not yet available in the United Kingdom, and the picture may have changed in the last 10 years. However, there seems to be sufficient evidence to regard possible asbestosis as significant disease, and therefore data on its relationship with exposure are relevant to hygiene standards. Of course, it is not the only or the most relevant index, and where data on mortality, in particular that due to lung cancer, are available, such data may be more appropriate. The mortality data available from the same factory have been discussed by Peto *et al.*³

In assessing the effects of long exposure to relatively low levels of asbestos, there is a wide range of possibilities for the health effect (TABLE 2). This wide range is not surprising since it is a result of attempting to extrapolate from shorter but higher exposures and because the most appropriate way of measuring exposure is not known. There are few data that would help to discriminate among the estimates of TABLE 2, and until better data are available, it has to be recognized that there is considerable doubt regarding the likely consequences of the current hygiene standard.

It is sometimes argued that because our knowledge is lacking, it is inappropriate to consider setting a hygiene standard or to review an existing standard. This is not a point of view to which we would subscribe. We must make the best use of our incomplete knowledge, recognize its limitations, and aim to produce better data for future assessment.

ACKNOWLEDGMENTS

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