

Occupational Health

THE HYGIENE STANDARD FOR CHRYSOTILE ASBESTOS*

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Summary Previous studies, including the analysis on which the current 2 fibres/cm³ hygiene standard is based, may have underestimated the risk of morbidity or mortality following exposure to low levels of asbestos dust. Accurate dose-response data at levels below 2 fibres/cm³ are unlikely to be available for the foreseeable future, and the biologically plausible assumption that excess cancer mortality is approximately proportional to dust level should be provisionally accepted. It may be reasonable, however, to postulate a safe threshold for mortality from asbestosis. If excess mortality from asbestos-related disease is proportional to dust level for each cause, approximately 10% of male asbestos workers might, under certain assumptions, eventually die of asbestos-induced disease after 50 years' exposure at 2 fibres/cm³. Peritoneal mesothelioma is usually due to crocidolite (blue asbestos) or other amphiboles, but exposure to chrysotile (white asbestos) alone may lead to a substantial risk of pleural mesothelioma. These predictions are based on rather small numbers in a single factory, and further studies in other working environments are required. Fibre counts based on optical microscopy are likely to be less relevant than total counts by electron microscopy, and excess mortality is virtually confined to men first exposed more than 20 years ago, when little or no accurate data on dust levels were collected.

THE PRESENT STANDARD

THE current hygiene standard of 2 fibres/cm³ for chrysotile asbestos dust was based on a study conducted in 1966 by the British Occupational Hygiene Society (B.O.H.S.).¹ Currently employed asbestos textile workers who had been exposed for at least 10 years were examined, and the prevalence of crepitations (basal râles) was related to cumulative dust exposure (fibre/cm³ years). A log-normal dose-response curve fitted the data adequately and led to the prediction that the cumulative dose corresponding to a 1% lifelong risk of developing crepitations was approximately 100 fibre/cm³ years, or 2 fibres/cm³ for 50 years (fig. 1).² Most men with cumulative exposures of less than 100 fibres/cm³ years had been employed for between 10 and 20 years at average dust levels of less than 10 fibres/cm³, and the absence of crepitations in this group was the basis for the prediction that the effect of 50 years' exposure at 2 fibres/cm³ would be minimal.

This prediction would be reasonable if crepitations

(an early sign of the effect of accumulated asbestos exposure) rarely appear or progress after exposure has ceased. However, other assumptions consistent with these data could lead to a predicted risk an order of magnitude higher than 1% following 50 years' exposure at 2 fibres/cm³. For example, suppose: (1) that pulmonary damage caused by inhaled asbestos dust is progressive, either because fibres remain in the lung or because the fibrosis they engender progresses after they have been eliminated; (2) that crepitations rarely appear less than 10 years after first exposure; (3) that men are usually removed from employment when they develop crepitations; and (4) that incidence (rate of appearance of new cases) is approximately proportional to cumulative exposure after an initial lag of 10-15 years. The B.O.H.S. study comprised all men who had started work since 1933, had completed 10 years' service, and were still employed in 1966. The proportion of men with crepitations rose from zero at exposures below 100 fibre/cm³ years to over 16% at 400 fibre/cm³ years. Under assumptions (1) to (4) the lack of cases in the lower-exposure groups might merely reflect a delay between first exposure and the appearance of crepitations, while the prevalence at 400 fibre/cm³ years would, if men were usually removed from employment within, say, 4 years of developing crepitations, suggest that the annual risk of developing crepitations after a cumulative exposure of about 400 fibre/cm³ years might be 4% per annum. (This figure depends on the average time from first detection of crepitations to early retirement, which has arbitrarily been taken to be 4 years. If employment normally continued for 8 years after the detection of crepitations the predicted incidence corresponding to 400 fibre/cm³ years would be roughly halved.) If incidence is proportional to cumulative dose the incidence at 2 fibres/cm³ might thus rise from zero during the first 10-15 years to about 1% per annum after 50 years, when the cumulative exposure would be 100 fibre/cm³ years. The risk of developing crepitations by retirement after 50 years' exposure at 2 fibres/cm³ would then be about 20%, and some further cases would appear after retirement. This figure is not presented as a useful prediction of the likely risk. It is intended only to illustrate the importance of the assumptions implicit in such extrapolation, particularly when prediction of the long-term effects of low exposure is based on initial response to relatively high exposure.

MORBIDITY AS A BASIS FOR A HYGIENE STANDARD

THE B.O.H.S. analysis is significant because it is the basis of the current standard. However, the risk of developing crepitations may not be an appropriate basis for a hygiene standard. The sign itself is virtually asymptomatic and may not progress to severe breathlessness or entail a substantially increased risk of bronchial carcinoma or mesothelioma. In the absence of direct observation of the prognosis in affected workers a standard based on such early signs may thus be unreasonably restrictive. Moreover, if data on severe disability or death are sufficient to evaluate the significance of the sign they will also be sufficient to assess the serious risk directly, so there may be little advantage in considering the prevalence of such a sign in framing a hygiene standard. This is not to say that such early signs are not

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Fig. 1-1
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Fig. 2-1
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with studying. They contribute to an understanding of the natural history of the disease process, and increased mortality in a small proportion of workers with crepitations can be detected and estimated before the overall excess approaches statistical significance.

It should also be pointed out that a 1% lifelong risk of developing such a mild condition may be too stringent a criterion.

THRESHOLD AND LINEAR MODELS FOR CANCER INDUCTION

Since the pragmatic implications of a non-linear dose-response model such as that in fig. 1 and the assumption of a threshold (absolutely safe level) are similar I shall apply the term "threshold" to both. The distinction is of scientific importance, but in the absence of biological understanding epidemiological data cannot establish whether a safe exposure level exists. Crump *et al.* argued on theoretical grounds that legislators should assume linear dose-response below the range of observation, even when the data suggest a quadratic model, particularly for carcinogens,¹ but for asbestos this is an academic point. The apparent threshold for crepitations could be an artefact for the reasons cited above, while

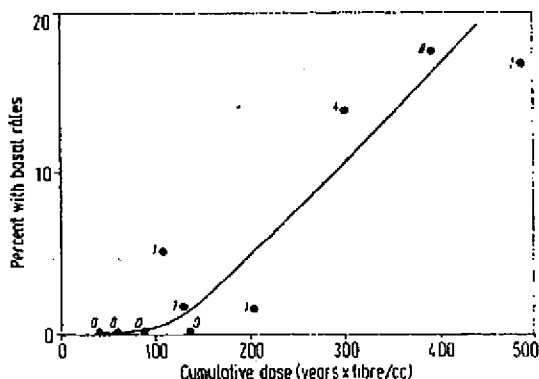


Fig. 1—Dose-response relationship for prevalence of basal rates in workers in a chrysotile asbestos factory (data from Berry¹). Log-normal curve. Numbers of cases in italics.

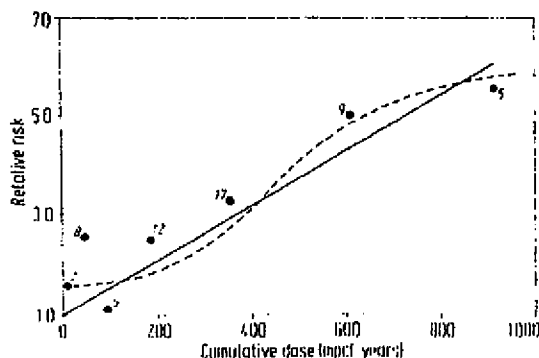


Fig. 2—Relative risk (observed/expected) for respiratory cancer in retired asbestos workers (data from Enterline *et al.*). ———— Original cumulative normal curve. Numbers of deaths in italics.

for lung cancer and mesothelioma there is neither theoretical nor statistical evidence to suggest that the relation between dose and response is anything other than linear.

PREVIOUS STUDIES RELATING CUMULATIVE EXPOSURE AND LONG-CANCER MORTALITY

The suggestion that the eventual proportional excess (relative risk minus one) of bronchial carcinoma is approximately proportional to cumulative asbestos exposure² is supported by published work. Enterline's data³ suggest such a linear relationship, but he rather arbitrarily superimposed a normal distribution (fig. 2) and concluded: "Had larger numbers been available it might have been possible to identify more precisely a T.L.V. (threshold limit value) for respiratory cancer in this type of population. The available data suggest, however, that large increments in respiratory cancer appear at a cumulative asbestos-dust exposure of somewhere between 100 and 200 mpcf-years." Similar data were reported by McDonald *et al.*⁴ These authors inferred that "excess mortality was virtually confined to men with exposure equivalent to at least 400 mpcf-years" and concluded that "considering all facets of disease—death, roentgenographic changes, pulmonary function changes, and respiratory symptoms—the 1% risk is reached by men in our third dust exposure category (100–200 mpcf-years)". However, a straight line appears to fit their data well (fig. 3), and the corresponding proportional excess of respiratory cancer at 150 mpcf-years—about 30%—would alone constitute a lifelong risk greater than 1%, ignoring morbidity and asbestosis mortality.

A cohort briefly exposed to amosite at the beginning of the 1939–45 war has been followed up by Scidman *et al.*⁵ This study is particularly valuable for testing models of the likely long-term effects of asbestos exposure, since the workers' cumulative doses (fibre/cm³ years or mpcf-years) have remained constant over more than 30 years, and the recorded duration of exposure, which was less than 2 years for most of the cohort, is probably closely proportional to cumulative dose. The relative risk for lung cancer rose for about 20 years and

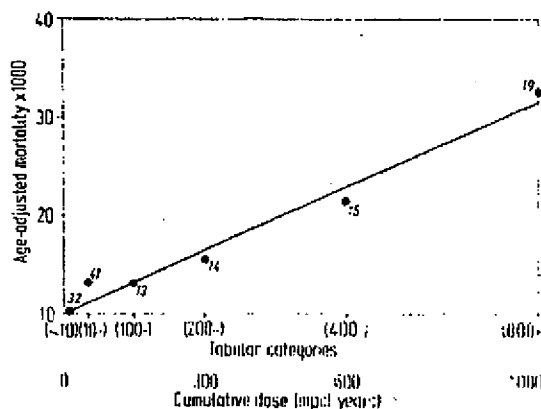


Fig. 3—Age-adjusted respiratory-cancer mortality in chrysotile mine and mill workers (data from McDonald *et al.*).

The highest category (800 or more mpcf-years) is plotted at 1000 mpcf-years. Other categories are plotted at their mid-range. Numbers of deaths in italics.

proportional to dust level these average levels can be related to overall excess mortality, as 100 men exposed to 1 fibre/cm³ and 100 at 3 fibres/cm³ would show subsequent excess mortality similar to that of 200 men exposed to 2 fibres/cm³ over a comparable period. Such aggregation is done implicitly in any study. Measured levels vary considerably over time in each area, so even a group nominally exposed to 2 fibres/cm³ will have experienced a wide range of dust levels. The excess risk appears to be largely confined to the period beyond 25 years after first exposure (table 1), when the excess mortality from respiratory disease, including bronchial carcinoma and mesothelioma, exceeded the expected mortality from all causes by 31% (19.26/61.44). The average exposure which caused this excess can be roughly summarised by total employment during the 30 years following first exposure. Table 11, which is based on the 158 men followed up for at least 30 years, suggests that this exposure consisted on average of about 11.6 years before 1954 at an average dust level of about 13 fibres/cm³ followed by 9.4 years at an average of about 5 fibres/cm³—a cumulative dose close to 200 fibres/cm³ years.

Dust levels in fibres/cm³ were estimated in each area from membrane-filter measurements at fixed sampling points from 1961 onwards. Thermal-precipitator measurements in particles/ft³ taken between 1951 and 1960 were converted to fibres/cm³ using the observed ratio of parallel measurements obtained by the two methods in 1960 and 1961. Routine measurements were not made before 1951. Estimated levels in

TABLE 11—EXPOSURE (TOTAL SERVICE IN SCHEDULED AREAS) IN MALE ASBESTOS TEXTILE WORKERS IN THE 30 YEARS FOLLOWING FIRST EXPOSURE*

Year of first exposure	No. of men	% distribution of total exposure (yr)				Average exposure (yr)	
		10–15	15–20	20–25	25–30	up to 1953 (approx. 13 fibres/cm ³)	from 1954 (approx. 5 fibres/cm ³)
1933–34	6	17	0	67	17	14.1	7.7
1935–39	104	25	19	19	37	12.0	9.3
1940–44	48	23	19	31	27	10.5	10.0
Total	158	24	18	25	33	11.6	9.4

* Men followed up for less than 30 years are omitted.

fibres/cm³ in each area of the factory are therefore based on direct observation after 1961 and conversion from particles/ft³ to fibres/cm³ between 1951 and 1960. Estimates before 1951 are based on the assumption that levels in each area fell from 1.5 times the 1951 values between 1933 and 1950. It is difficult to assess the error in this factor. Excess mortality does not appear to have been much higher in men first employed between 1933 and 1950 than among those first employed after 1950,¹⁰ and in view of the technical continuity in many areas between 1933 and 1950 it was considered likely that dust levels did not fall substantially over this period. However, this crucial assumption is open to dispute and cannot be proved until further follow-up has provided a more accurate estimate of excess mortality in more recent employees. Exposure was predominantly to chrysotile, although a small proportion of the fibre processed was crocidolite at various times after 1933.

BRONCHIAL CARCINOMA

Mortality due to lung cancers other than pleural mesothelioma in this cohort has been approximately twice the national average beyond 25 years after first exposure (14 observed; 6.57 expected). There is no evidence that the relative risk increases beyond 25 years, which perhaps reflects the relatively negligible increase in cumulative dose in recent years. Dust levels in this asbestos textile factory have been much reduced

since 1955. This interpretation is supported by an earlier study. Pre-1933 workers, who were exposed to very high levels before 1933 and comparatively low levels subsequently, showed a similar lack of progression beyond 20 years for both bronchial carcinoma and asbestosis mortality.¹¹ If the eventual proportional increase in mortality due to bronchial carcinoma is approximately linearly related to cumulative exposure and the risk is doubled at 200 fibres/cm³ years, a level of 1 fibre/cm³ might, after 50 years' exposure, increase mortality due to this cause by 25% after retirement, corresponding to a lifelong risk of bronchial carcinoma attributable to asbestos of about 3% in smokers.⁶ The risk to non-smokers is probably very small. Asbestos and cigarette smoking appear to enhance each other's effects in causing bronchial carcinoma,¹² but mortality due to this cause is so low in asbestos workers who have never smoked that the risk due to asbestos cannot be estimated with any confidence from published work.

A MORE GENERAL LINEAR MODEL FOR BRONCHIAL CARCINOMA

This analysis is based on the assumption that the relative risk for bronchial carcinoma is increased in proportion to cumulative dose. As this is not precisely true a less restrictive assumption may be preferable. Bronchial carcinoma accounts for an approximately constant proportion of male deaths in England and Wales (12% at age 50–54, falling to 10% at age 70–74), and various studies suggest that the relative risk for this cause does not fall with the passage of time after exposure to asbestos has been substantially reduced or ceased. The observed excess mortality due to bronchial carcinoma as a proportion of total expected mortality beyond 25 years (7.43/61.44, or 12%) is therefore a reasonable estimate of the lifelong attributable risk in this cohort. It would follow, under any model which predicts that the increase in risk is approximately proportional to dust level, that a similar period of exposure at a reduced dust level would produce a proportionately lower risk. Thus a group that had on average been exposed to 1.3 fibres/cm³ rather than 13 fibres/cm³ for about 12 years followed by 0.5 fibres/cm³ rather than 5 fibres/cm³ for about 9 years would probably have a lifelong attributable excess risk due to bronchial carcinoma of about 1.2%. The conclusion that about 20 years' exposure at about 1 fibre/cm³ is likely to cause bronchial carcinoma in roughly 1 man in 100 thus follows from any linear model, but a more specific assumption is required to predict the effect of 50 years' exposure.

PLEURAL MESOTHELIOMA

As only 5 cases of pleural mesothelioma have occurred in this group, any model-fitting or extrapolation must be very speculative. These 5 cases are tabulated by man-years of observation in table 1, which suggests that incidence rises sharply with increasing time since first exposure. A formal residence-time model with linear dose response for cancer incidence is given by the equation:

$$\text{Incidence at time } T \text{ after first exposure} = \frac{k}{T} \int_0^T c(t) dt$$

where $c(t)$ is the dust level at time t . The value $k = 2$ fits the incidence rates in table 1 well and corresponds closely to Newhouse and Berry's finding that incidence rose as $(t - 9)^2$ after heavy mixed exposure to chrysotile and crocidolite had ceased.^{13,14} Applying the observed rates in table 1, the predicted

* Diseases for which the excess risk persists beyond retirement cannot be summarised by relative risk or cumulative prevalence at a particular age. The appropriate statistic is the proportion who will eventually die of the disease as a result of their exposure. This is described throughout as the "lifelong risk".

prevalence after 50 years' exposure at 1 fibre/cm³ corresponding to this model is 1.6%.

The corresponding lifelong attributable risk to a man exposed to 1 fibre/cm³ from age 15 to 65 is approximately 2%. It must be emphasised that this estimate is necessarily unreliable. It is based on only 5 cases, and 2 of these were in men employed in an area where raw asbestos was handled who should perhaps be excluded from the calculation, almost halving the predicted risk.

BRIEF OR NON-OCCUPATIONAL EXPOSURE

Malignant diseases such as mesothelioma or bronchial carcinoma for which the incidence rises as the third or higher power of time since first exposure to a carcinogen cannot be understood without such formal analysis. For example, there had up to the end of 1975 been 10 cases of pleural mesothelioma among approximately 20 000 men first employed in this factory after 1933. To express this as a risk of 0.05% is meaningless. The lifelong risk to a man employed continuously since 1933 may exceed 10%. On the other hand, the suggestion that brief exposure is extremely dangerous is equally misleading. Preliminary results of a study including the entire past and present workforce support the suggested model, and only 1 case is known to have occurred in approximately 15 000 men exposed for less than 2 years since 1933. Isolated case-reports with a history of minimal exposure must be viewed against some hundreds of thousands of men and women with slight occupational exposure and several millions with casual non-occupational exposure. A recent study confirming that the risk of mesothelioma is dose-related suggests that only very high dust levels produce an appreciable risk after brief exposure.¹⁵

MINIMAL CROCIDOLITE EXPOSURE IN CHRYSOTILE WORKERS

It has been argued that pleural mesothelioma is due to crocidolite even when it occurs in workers whose exposure has been largely to chrysotile with minimal exposure to other fibres. Evidence from three sources appears to contradict this interpretation: (1) 9 cases⁶ have occurred in Canadian chrysotile miners and millers with no exposure to crocidolite;¹⁶ (2) the incidence in our study has been comparable to that in Newhouse and Berry's¹⁷ cohort of workers with heavy crocidolite exposure. Their data show a clear dose-response for both severity and duration of exposure. Although average exposures were longer in our cohort, total exposure to crocidolite was so much lower that the risk of mesothelioma should have been far less than that observed in the factory we studied if crocidolite were the sole cause of mesothelioma; (3) workers exposed to crocidolite show a comparable incidence of peritoneal and pleural mesothelioma. For example, 22 of the 45 mesotheliomas reported by Newhouse and Berry¹⁷ were peritoneal in origin. None of the 34 that have occurred in workers in the factory we studied (including women and pre-1933 employees) or the 9 cases in Canadian miners and millers were peritoneal. An obvious explanation for this difference is that chrysotile causes only pleural mesothelioma, whereas crocidolite causes both pleural and peritoneal tumours.

ASBESTOSIS

The lifelong risk of death from asbestosis following exposure to 1 or 2 fibres/cm³ cannot be predicted with any confidence. There are no grounds for assuming linear dose-response for such a generalised progressive disease, and although a qualitative dose-response has been demonstrated at very high exposure levels¹⁸ there may well be a safe or virtually safe thresh-

old. There were 17 deaths (9.17 expected) due to non-malignant respiratory disease over 25 years after first exposure in our study, including 5 attributed to asbestosis. If it is assumed that incidence is proportional to cumulative dose, the corresponding life-long attributable risk after 50 years' exposure at 1 fibre/cm³ would exceed 1%,⁹ but this model is presented for lack of another rather than because it is particularly plausible biologically. Further data on early pulmonary signs may indicate whether a threshold exists, but even if the incidence of crepitations is linearly related to dust level the prognosis in affected workers may be related to the severity of preceding exposure.

DISCUSSION

There have been too few deaths in our study to estimate the risks or evaluate the suggested models adequately for each asbestos-related disease, but the overall excess is substantial. There were 80 deaths (61.44 expected) more than 25 years after first exposure, including 14 (6.57 expected) due to bronchial carcinoma, 17 (9.17 expected) due to non-malignant respiratory disease, and 4 due to pleural mesothelioma. The excess for asbestos-related disease thus exceeds the overall expected number by about 30%. The implications of these figures are perhaps obscured by the necessarily complex statistical models presented for each separate cause. If dose-response were linear for all causes (i.e., the risk of death due to asbestos exposure were proportional to dust-level for any given period of exposure) it would follow that about 20 years' exposure at about 1 fibre/cm³ would increase total mortality by about 3% 25 years after first exposure. The trend in the right-hand column of table 1 suggests that this proportional excess is likely to persist with the further passage of time, so such exposure might be expected to lead to fatal asbestos-induced disease in about 3% of men. The assumption of dose-linearity is dubious for asbestosis mortality, but both epidemiological findings and contemporary knowledge of carcinogenesis suggest that excess mortality from bronchial carcinoma and pleural mesothelioma is likely to be proportional to dust level.

These predictions might be grossly inaccurate. Individual cases have not been investigated in detail, and previous employment in dusty working environments may have contributed to the excess mortality in this cohort. Employment histories are now being re-examined, but the estimates of pre-war asbestos exposure are not reliable, and the assumption that there is no safe threshold cannot be confirmed without long-term prospective observation of workers exposed to low levels. The recent I.A.R.C. monograph on asbestos,¹⁷ which provides a comprehensive reference source and summary of recent work, concludes that "at present, it is not possible to assess whether there is a level of exposure in humans below which an increased risk of cancer would not occur." There are thus three alternatives:

1. To conclude that the economic consequences of more restrictive legislation are not justified unless a further 15 or more years' observation of workers exposed to low levels of pure chrysotile shows the current standard to be dangerous.

2. To base a decision on these analyses, ignoring sampling error, our results suggest that about 5-10% of men exposed for 50 years to chrysotile asbestos concentrations of 1-2 fibres/cm³ are likely to die of asbestos-induced disease. Plans

¹ Assuming that 1.2 and that incidence 30 years after first exposure following 11-2 years at 1.3 fibres/cm³ and 9-4 years at 5 fibres/cm³ (table 1) is 3 per 1000 per annum, table 1, col. 5. The model can be justified biologically, but for practical purposes it is irrelevant whether incidence rises roughly as t^3 , as the model predicts, or as $t^{1.9}$. These factors are closely proportional for values of t between 20 and 50 years, and below 20 years the model is negligible.

² A further mesothelioma occurred in a woman in this population who had previously been exposed to crocidolite.

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