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Asbestosis: a study of dose-response relationships in an asbestos textile factory

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ABSTRACT A group of 379 men who had worked at an asbestos textile factory for at least 10 years has been followed up. The prevalence of crepitations, 'possible asbestosis', certified asbestosis, small opacities in the chest radiograph and values of lung function have been related to dust levels. The type of asbestos processed was predominantly chrysotile although a substantial amount of crocidolite had also been used in the past. There was a higher prevalence of crepitations than had been observed previously at the same factory. The presence of crepitations is not a specific effect of asbestos exposure and 'possible asbestosis', a combined judgement of two physicians on whether a man had developed signs which might be attributable to early asbestosis, was preferred. Fifty per cent of men with a diagnosis of possible asbestosis were certified as suffering from asbestosis by the Pneumoconiosis Medical Panel within 3-5 yr. The most reliable data relate to men first employed after 1950; 6·6% of men in this group had possible asbestosis after an average length of follow-up of 16 yr and an average exposure to 5 fibre/cm³ where the dust levels were determined by static area samplers. The forced expiratory volume and forced vital capacity declined significantly with exposure, after allowing for age and height, but there was no decline in the total lung capacity. The transfer factor also declined with exposure, but not to a statistically significant extent. The non-smokers and light smokers as a group had less crepitations, asbestosis and small opacities on the chest radiograph than heavier smokers with similar exposure. Combining dust concentrations to form the cumulative dose may not be completely satisfactory, and a family of measures was investigated which allows for elimination of dust from the lungs and includes the cumulative dose as a special case. Because the rate of elimination of dust from the lungs is unknown, and cannot be estimated from the data, this approach leads to a wide range of possible interpretations of the data; for example the concentration such that possible asbestosis occurs in no more than 1% of men after 40 years' exposure could be as high as 1·1 fibres/cm³ or may have to be as low as 0·3 fibres/cm³. This range is wide because the data relate to higher dust levels, and a shorter period of follow-up. Until data are available on groups exposed to lower levels it will not be possible to assess the effects of the current standard with any certainty. However, the results of this study show that it is important to continue to reduce dust levels to values as low as possible.

In 1968 the British Occupational Hygiene Society (BOHS) published hygiene standards for chrysotile asbestos dust (British Occupational Hygiene Society, 1968). One of the features was that risk was related to accumulated exposure, that is the sum of concentration × period of exposure to that concentration over the whole period of exposure. With an accumulated exposure of 300 fibre/years/cm³ it was concluded that it was probable that the risk of contracting asbestosis would be less than 1%, where asbestosis was defined as the earliest demonstrable effect on the lung attributable to asbestos and this effect was the presence of persistent basal rales. The recommendations were made with two main notes of caution. First, it was pointed out that few

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the periodic examinations and which men had been certified as having asbestosis, together with the date of certification and degree of disability. Information on certification is complete up to 1975 on all men, including those who had left the factory.

The diagnosis of asbestosis is based upon the presence of physical signs of pulmonary fibrosis, radiological appearance and lung function defects. McVittie (1965) indicated that the Pneumoconiosis Medical Boards diagnosed asbestosis in the presence of a history of adequate exposure, on the finding of end-inspiratory basal rales, finger clubbing, radiological abnormality and reduction of lung function such as transfer factor and vital capacity. Adequate exposure plus two of the other relevant criteria listed above is sufficient for diagnosis but the Board must be satisfied that the individual is disabled, before certifying asbestosis.

It has been the practice of the factory medical officer to examine all asbestos workers routinely every two years, and to advise them to change to less dusty jobs if he believes that they are developing symptoms or signs of early asbestosis. He bases his suspicions on the finding of basal rales or crepitations, radiological changes of varying degree, a falling gas transfer factor, and restrictive changes in lung volume or ventilatory capacity. This condition is referred to as 'possible asbestosis' and is a diagnosis based on signs insufficient to warrant Disablement Benefit. The company has supported this policy by paying workers with possible asbestosis, who change jobs, a guaranteed basic wage plus an ex gratia payment.

Workers were given chest radiographs every three years from 1951 until 1967 and every year since then. Lung function tests were introduced in May 1967 and are carried out every two years.

The most recent radiographs were read in random order, and without knowledge of the men's identities or job histories, by four readers independently using the ILO/UC 1971 classification (International Labour Office, 1972). The four readings of small opacities were combined by scoring the categories 0/0, 0/1, . . . , 3/4 as 0, 1, . . . , 10 and taking the average score. In most instances the profusion of irregular opacities exceeded that of rounded opacities, but whichever type gave the higher reading was that which was averaged; there were only five films in which the profusion of rounded opacities was the greater, and in all of these the average profusion was 0/1 or less.

The factory medical officer had originally diagnosed 60 cases of possible asbestosis. A clinician (JCG) reviewed the medical data for each man without knowing his occupational history, and noted where his opinion on the presence or absence of possible asbestosis differed from that of the factory medical officer. There were 12 men, placed by the latter in the possible asbestosis group, but for whom none or only one reader had recorded a profusion of small opacities of 1/0 or more, and there were 37 men whom only the clinician had placed in this group, for whom at least two readers recorded 1/0 or more. The clinician and factory medical officer examined the complete medical files of these 49 men together and reached agreement on a diagnosis. Seven men were removed from the possible group and five were added to it. The most common reason for considering a case not to be possible asbestosis was that it was thought more likely that the signs were attributable to other disease. This shows that the diagnosis of asbestosis cannot be made without considering all the clinical evidence, and sole reliance cannot be placed on any single feature used for diagnostic purposes.

DUST EXPOSURE

Details of all the jobs performed by each man were noted by an independent industrial hygienist (SAR) who visited the factory and examined the employment records. In all, 236 job descriptions were used. For each job description a dust level was calculated for each year by taking the average of the levels measured at the static dust sampling locations in the area where the job was carried out. In all, 84 sampling locations had been used over the period 1961–72.

Fibre counts were not available for 1951–60, but thermal precipitator particle counts were available for 1952 and 1960. The fibre counts for 1951–55 were taken as those of 1961 multiplied by the ratio of the 1952 to the 1960 thermal precipitator measurements. This ratio was dependent on job, ranging from 1·4 to 3·4 (British Occupational Hygiene Society, 1968). The counts for 1956–60 were taken to be the same as 1961–65. There were no dust measurements before 1950. For 1933–45 the concentrations were taken to be 1·5 times those in 1951 and for 1946–50 as 1·25 times the 1951 values. These concentrations, particularly for the early years, are probably underestimates of the actual concentrations (British Occupational Hygiene Society, 1968).

Some men were coded as doing more than one job at the same time; the dust level in these cases has been taken as the mean of the concentrations for the different jobs. When a man was away from the factory, or at the factory but working in a job away from the production area, it was assumed that he was not exposed to asbestos.

As an indication of the dust conditions within the factory Table I gives the mean dust level and the percentage of men in the study within the ranges

SC-UK-MS-000062

Table 2 *Summary of exposure at factory*

Exposure factors	Workers first employed before 1951		Workers first employed after 1950	
	Total	With signs	Total	With signs
Year started at factory				
1931–35	61	7	—	—
1936–40	50	15	—	—
1941–45	38	15	—	—
1946–50	93	23	—	—
1951–55	—	—	109	22
1956–60	—	—	78	6
1961–65	—	—	23	2
Maximum annual time-weighted average concentration (f/cm³)				
<5	1	0	15	1
5–9·99	98	9	85	9
10–19·99	70	26	92	18
20–39	73	27	12	2
Cumulative exposure* (f/cm³/yr)				
<50	3	1	36	4
50–99	23	6	93	12
100–149	36	12	52	23
150–199	44	27	34	1
200–249	39	33	—	—
250–299	33	33	—	—
Time since first employed at factory* (yr)				
<10	1	0	9	3
10–14	0	0	24	16
15–19	37	12	} 174	13
20–24	65	19		
25–29	53	56		
30–39	43	33		
Age* (yr)				
<40	3	0	36	0
40–44	5	0	23	3
45–49	22	8	31	4
50–54	14	17	35	6
55–59	32	22	33	13
60–72	66	19	39	8
Total	182	62	197	36

*For those with signs, these are calculated up to the first occurrence of the signs.

Table 3 *Number of men with crepitations recorded by factory medical officer or by Pneumoconiosis Medical Panel*

Examiner and opinion			
Pneumoconiosis Medical Panel	Factory medical officer Yes	No	Total
Yes	51	27	78
No	31	268	299
Total	82	295	377

in whom crepitations were heard at the factory but were not heard by the PMP.

RELATIONSHIP BETWEEN POSSIBLE ASBESTOSIS AND CERTIFICATION

Except for the one man who was certified after death, and had not been seen in the factory medical department within the previous 10 years, all the certified cases were also in the possible category. An analysis, using life-table techniques, has been carried out on the interval between suspicion and certification. The results are given in Figure 1, which shows the cumulative percentage of certified cases plotted against time since suspicion; 25% became certified within 15 months of suspicion and 50% within 3·5 yr. Of 19 men who were uncertified after five years' follow-up since first suspicion, only one was subsequently certified in, on average, a further two years' follow-up.

RADIOLOGICAL FINDINGS, LUNG FUNCTION AND EXPOSURE

The profusion of small opacities and bilateral pleural thickening have been related to cumulative dust exposure (Table 4). Again, these data cannot

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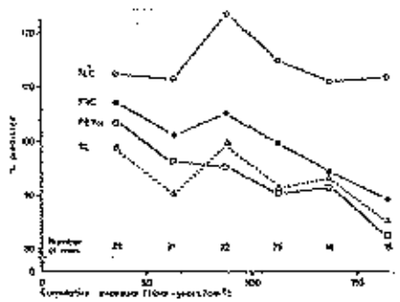

Fig. 3 The relationship between indices of lung function and cumulative exposure to asbestos, for men first employed after 1950.

the non-smokers were on average younger than the smokers, aged 55 years compared with 58 years for those first employed before 1951, and 47 years compared with 52 years for those first employed after 1950. The data are shown in age groups in Table 7. After taking account of age, there were significantly fewer signs in non-smokers and light smokers than in heavier and ex-smokers, for men first exposed after 1950: for crepitations, $P < 0.01$; for possible and certified asbestosis, $P < 0.1$ and for small opacities $P < 0.05$.

Dose-response relationships

The dose-response relationships considered in this section are those between the prevalence or incidence of one of the three signs (crepitations, possible, or certified asbestosis) and a measure of dust exposure. The mathematical forms of dose-response relationships and a discussion of methods for combining the

Table 6 The association between smoking and signs of asbestosis

Employment group and smoking habit	Mean cumulative exposure (fibre-years)	Numbers of men				
		Fatal	Crepitations	Possible asbestosis	Certified asbestosis	Small radiological opacities*
First employed before 1951						
Never smoked	197	23	4	3	3	4
1–4 cigarettes/day	309	7	2	3	1	2
5–14 cigarettes/day	188	62	22	15	7	35
15+ cigarettes/day	197	82	30	18	9	32
Ex-smokers	192	28	7	6	3	13
First employed after 1950						
Never smoked	79	42	0	0	0	2
1–4 cigarettes/day	93	13	0	0	0	0
5–14 cigarettes/day	89	68	11	6	5	11
15+ cigarettes/day	84	68	11	4	3	11
Ex-smokers	91	26	4	3	2	4

*Profusion 1/0 or more.

Table 7 The association between smoking, age and signs of asbestosis

Employment group and smoking habit	Age group	Numbers of men				
		Fatal	Crepitations	Possible asbestosis	Certified asbestosis	Small radiological opacities*
First employed before 1951						
Never smoked and 1–4 cigarettes per day	−54	14	0	0	1	0
	55+	18	7	6	2	6
Other smokers and ex-smokers	−54	57	7	5	2	6
	55+	115	42	24	19	47
First employed after 1950						
Never smoked and 1–4 cigarettes per day	−44	26	0	0	0	1
	45–54	12	0	0	0	0
	55+	12	0	0	0	1
Other smokers and ex-smokers	−44	32	0	0	0	1
	45–54	31	8	3	4	10
	55+	37	33	8	6	13

*Profusion 1/0 or more.

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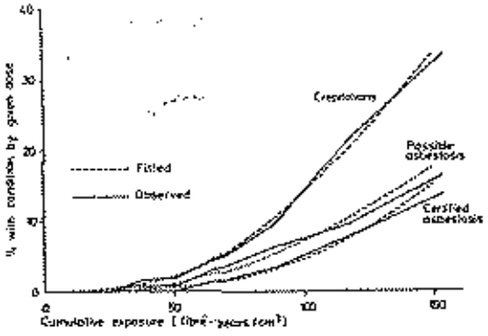

Fig. 4 *The relationships between the percentage developing the conditions, crepitations, possible asbestosis and certified asbestosis, and cumulative exposure to asbestos, for men first employed after 1950. The observed relationships were obtained by life table methods.*

and certified asbestosis the 1% prevalences correspond to 50 years' exposure to 0·19 and 0·37 f/cm³ respectively.

Thus, the choice of a suitable measure of exposure is highly critical, and it is not known what measure is most appropriate. If, over a long period, dust is eliminated from the lungs at a rate proportional to the amount present, and disease is caused by cumulative dose weighted by residence time of each contribution, then a family of exposure measures is produced. This family is indexed by the rate of exponential elimination, or half-life time, and, as extreme cases, contains the cumulative dose (half-time zero) and the cumulative dose weighted by time since exposure (half-time infinity). Further details are given in the Appendix.

This family of curves has been fitted to crepitations and *possible asbestosis for a number of half-life* times for men first employed after 1950. It was impossible to estimate precisely the half-life time giving the best fit to the data, and any value in excess of three years was considered to be adequate. Failure to estimate the half-life time reliably is not surprising, because the critical data would be observations on men who had left the factory many years previously.

Another way in which the exposure measure may be inappropriate is that a given dose is assumed to be effective immediately. The measure can be amended to accommodate a lag period for the development of an observed effect by assuming that, however severe the exposure, *disease is not* observed until some minimum time has elapsed since the start of exposure. There are insufficient data to estimate this lag period and the model was fitted incorporating a lag of five years.

Cumulative dose is correlated with years since first exposure; using this time as a measure of dose gives just as satisfactory a fit to the data as using cumulative dose and its generalisations; *however, taking account of the dust level is more* appropriate biologically.

ALTERNATIVE DOSE-RESPONSE MODEL

The dose-response model used has a reasonable biological basis, but other models may be appropriate. An alternative is that the incidence rate of diagnosis of an adverse effect is proportional to the amount of dust in the lungs (see Appendix). The analyses have been repeated with this model, which was satisfactory for the case with a five-year lag provided that the half-life was at least five years.

IMPLICATIONS FOR MODERN CONDITIONS

The disease pattern observed in this study has occurred as a result of higher dust levels than those which occur now (Table I). It is interesting to predict the likely disease pattern with current standards and the concentrations estimated to result in a given percentage of men with disease. This has been done for continuous lengths of exposure of 30, 40 or 50 years. The percentage of men estimated to have reached the possible asbestosis category by the end of a period of exposure at 2f/cm³ has been calculated and, in addition, the concentration necessary to limit this percentage to 1% has been estimated. These calculations have been based on the parameter estimates from the *post-1950 group for both models for a range of* values of the half-life time of dust elimination (Table 8).

Varying the half-life time of dust elimination has a marked effect. For example, after 40 years exposure to 2f/cm³, and using the logit dose-respons

SC-UK-MS-000068

Most of the men in the study had been employed elsewhere before starting work at the factory; only 40% started before age 30. Of the 13 men in the post-1950 group who had possible asbestosis, five had worked in the cotton industry. One of these had been a stripper and grinder for 20 years and was considered to have reached the possible asbestosis category within eight years of first employment at the factory studied, the only sign within 10 years (Table 2). Another man who was certified as suffering from asbestosis after 12 years in the factory had previously been a chemical worker for 20 years; asbestosis was not confirmed at death. It seems likely, therefore, that some of the signs observed in this study were at least partly attributable to previous employment in other dusty occupations.

The association between smoking and signs of asbestosis (Table 6) is in agreement with Weiss (1971) who found pulmonary fibrosis in the chest radiograph in 40% of smokers and 24% of non-smokers among workers exposed to chrysotile asbestos.

The data have been analysed in terms of a family of exposure measures, an inherent feature of which is that there is the equivalent of an exponential decline in the amount of active material. This could arise as a result of both elimination of dust and a reduction in activity of the dust remaining. Beattie and Knox (1961) determined the mineral content after death in lungs of workers from the factory, and found no evidence of a decline in the first eight years after exposure had stopped. However, they took no account of changes in dust level; those who had survived for a period after leaving the factory were, on average, probably first exposed about 15 years earlier than those who died while still employed, and 70% of the men in the study had been employed before 1932. There is evidence that trace metals are leached from chrysotile asbestos *in vivo* (Morgan *et al.*, 1971; Morgan *et al.*, 1973). This leaching, and other changes within the lungs, may reduce the hazard of the remaining material. The range of measures was introduced because it was felt that the simplest measure, that of cumulative exposure, might not be completely satisfactory because of its inability to allow for the possibility of development of disease after exposure has ended. Crepitations appeared to develop in five men while they were not exposed, but in two of these the change could have been caused by observer differences. The changes in the other three men could have been attributable to the transient nature of the sign or to reasons other than asbestos exposure.

Because so few of the men have been retired for even five years, we are unable to discriminate between the different dose-response relationships. Data of this type from other sources would provide clues to the most appropriate value of the half-li time of dust elimination. If elimination were slo then cases of asbestosis would be first diagnos and certified in men who left the industry ma years earlier; if this were not the case, then the u of cumulative dose would be reasonably valid. It known that an excess incidence of lung cancer a mesothelioma occurs in men many years after t end of exposure (Newhouse, 1973) but informati is lacking on the diagnosis of asbestosis in form asbestos workers.

There are several reasons why the models mig be inappropriate. First, if the diagnostic procedu were not uniform over the period 1961–73, th some of the recorded new cases could be attributa to a change in diagnostic criteria rather than to t clinical changes. The factory medical officer w replaced during this period and, in addition, l function testing was introduced at about the sa time. Second, the assumption that the amount dust deposited in the lungs is a fixed proportion of t airborne concentration would not be valid if th had been changes in the particle size in the airbo dust cloud during the period 1951–72. In view of t changes in dust levels over this period, a change the size distribution would not be surprising; ho ever we have no relevant data.

A dose-response relationship between morbid and asbestos exposure has been considered in t other studies. McDonald *et al.* (1974) studi several facets of disease, death, radiological chan pulmonary function changes and respiratory sy toms and related these to the cumulative expo measured as millions of particles per cubic t times years (mpcf-yr). They concluded that th was a 1% risk of acquiring clinically signific disease for an exposure between 100 and 200 mpcf-Some of their observations were based on a comp cohort but others only on current employees. W *et al.* (1975) considered lung function measureme and irregular small opacities on the chest radiogra and found little evidence of a dose-response relat ship below 100 mpcf-yr. Using the results of si taneous sampling with the impinger and f counting method they equated this dose t 200 f-yr/cm³. Their observations were based current employees only, and for some, expos had started only shortly before the study.

The results of the present study are disappoin in that it is not possible to draw any definite c clusions on the effects of the present 2f/cm³ stand Comparison of the present results with those g earlier (British Occupational Hygiene Society, 1 Berry, 1971) shows that there is a higher preval of crepitations at any dose than was obta previously. However, in view of the doubt

SC-UK-MS-000070

evaluated. In this example some of the concentrations could be zero to cope with a break in exposure, c_2 or $c_3 = 0$, or with retirement, $c_4 = 0$. Then the cumulative dose is given by:

$$\text{cumulative dose} = c_1t_1 + c_2(t_2 - t_1) + c_3(t_3 - t_2) + c_4(t_4 - t_3)$$

This is how the cumulative dose would be evaluated in practice, but to simplify a more general approach it may also be written as an integral. Suppose exposure started at time zero and is to be evaluated up to time t, and that the concentration at time u is $c(u)$ for $0 \leqslant u \leqslant t$; again $c(u)$ would be zero during breaks in exposure or after retirement. Then

$$\text{cumulative dose} = \int_0^t c(u)\,du$$

This measure attaches no more importance to exposure a long time ago than to recent exposure, *and does not alter after exposure* has ended. Both of these properties are unrealistic for a disease, such as asbestosis, which is dependent more on early exposure than on recent exposure and which may develop after exposure has ended. The simplest way of allowing for both of these points was given by Jahr (1974) who suggested that each component of exposure should be weighted by the time which has elapsed since the exposure occurred. Thus, cumulative dose weighted by time since exposure is given by

$$\int_0^t (t - u)\,c(u)\,du$$

and, in practice, evaluated by summing contributions *of the form*

$$c_2(t_2 - t_1)\{t - \tfrac{1}{2}(t_1 + t_2)\}$$

over each period of exposure to a fixed concentration.

The weighting factor could be regarded as the time that the dust has been in the lungs if elimination has not taken place. Looking at the measure in this way, and postulating that elimination does occur, leads to a generalisation.

Suppose that, over the long term, dust is eliminated from the lungs at a rate proportional to the amount in the lungs, and the constant of proportionality is λ; in other words, in the absence of further exposure the amount of dust in the lungs declines exponentially at rate λ and will be reduced to one half of its level in time $T = \ln 2/\lambda$, the half-life time. The actual amount of dust deposited in the lungs is unknown, but is assumed to be proportional to the concentration. Then the amount of dust in the lungs at time t is, apart from a constant of proportionality, $A(t)$ given by:

$$A(t) = \int_0^t c(u)\,e^{-\lambda(t-u)}\,du$$

If it is supposed that each component of dust which was deposited in the lungs contributes to the dose for the time it remains in the lungs then the dose $D(t)$ evaluated at time t is given by:

$$\begin{aligned} D(t) &= \int_0^t A(v)\,dv \\ &= \int_0^t \int_0^v c(u)\,e^{-\lambda(v-u)}\,du\,dv \\ &= \int_0^t c(u) \int_u^t e^{-\lambda(v-u)}\,dv\,du \\ &= \frac{1}{\lambda}\int_0^t c(u)\{1 - e^{-\lambda(t-u)}\}\,du \end{aligned}$$

This is the generalised measure which, except for infinite λ, has the properties that, first, it gives more weight to exposure a long time ago than to recent exposure and, second, it continues to increase after exposure has ended. If λ tends to infinity then D tends to zero, but in such a way that λD tends to cumulative dose. Thus, in effect the cumulative dose may be considered as a special case of the generalised dose when elimination of dust from the lungs takes place very quickly. If λ tends to zero, then D tends to the cumulative dose weighted by time since exposure which, therefore, is also a special case of the generalised measure when there is no elimination of dust from the lungs.

To summarise, the generalised measure consists of a family of dose measures with each member of the family defined by the parameter λ, or, in an equivalent manner, by the half-life time T. The full family *is obtained by allowing* T *to vary from zero to* infinity. The approach followed here is akin to that of the British Thoracic and Tuberculosis Association (1975).

DOSE–RESPONSE RELATIONSHIPS

If P is the prevalence of a sign at dose D, the dose-response relationship is defined by a functional relationship between P and D, that is, $P = f(D)$. All the relationships considered are such that P is zero when D is zero, and as D increases above zero *then so also does* P; this excludes relationships

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period by maximum likelihood because of the sudden changes in the concentrations when a man changed jobs. This meant that L was not differentiable with respect to w and prevented the application of maximum likelihood theory. However a graphical comparison of the observed and fitted dose-response relationship suggested that there were insufficient data to discriminate between the model without a lag period and one with a lag period of five years. The lag period cannot be much more than five years as there was one case of possible asbestosis only 7·25 yr after first exposure.

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