Asbestos

Effects on health of exposure to asbestos

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Richard Doll and Julian Peto

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EFFECTS ON HEALTH OF EXPOSURE TO ASBESTOS

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2 Medical effects of asbestos

Knowledge of the medical effects of asbestos has accumulated slowly since the turn of the century and it is now universally agreed that the exposure of men and women to asbestos fibres can, in certain circumstances, lead to three diseases: asbestosis, lung cancer, and mesothelioma of the pleura or peritoneum. It can certainly also cause a group of benign conditions of the pleura of variable importance, and it may cause a group of other cancers, including cancers of the larynx, gastro-intestinal tract, and kidney, and conceivably a wide range of others. Some of the features of these conditions are, we believe, beyond dispute and we describe them briefly here, without giving detailed evidence in support. Contentious matters (of which there are many) are left to later chapters.

Benign conditions of the pleura

The benign conditions of the pleura that are produced by asbestos are seldom of any lasting importance. Pleural effusions may cause temporary disability, but they invariably resolve. Diffuse pleural thickening, which may follow an effusion or may develop without an effusion ever having been detected, is usually asymptomatic. It may rarely cause constriction of the lungs with impairment of function and, in extreme cases, consequent disablement. Lesser degrees of thickening, diagnosed radiographically, provide suggestive evidence of exposure to support the diagnosis of asbestos-induced disease in the lungs or elsewhere. They can, however, be produced in other ways and are far from diagnostic. Calcified pleural plaques, which are strongly indicative of exposure, are late findings and no help in the diagnosis of early cases. None of these benign pleural conditions will be considered further.

Asbestosis

Asbestosis was defined by the Advisory Committee on Asbestos (1979) as "fibrosis of the lungs caused by asbestos dusts which may or may not be associated with fibrosis of the parietal (outer) or pulmonary (inner) layer of the pleura." The symptoms attributable to it (shortness of breath and cough) can be produced in many other ways, and the diagnosis during life is made on the physical signs, the results of pulmonary function tests, and the radiographic findings, accompanied by a history of substantial exposure. The fibrosis of the lungs that is associated with asbestosis is, however, indistinguishable radiologically from cryptogenic fibrosing alveolitis (an uncommon disease of unknown cause*) and the differential diagnosis is a matter of weighing probabilities. It is seldom difficult with a clear history and advanced disease. There may be great difficulty, however, in diagnosing the disease in its early stages, as there is no sharp point in the development of signs and symptoms at which it can be said that a change in state from healthy to diseased has occurred. The clinical diagnosis is, therefore, a matter of judgment and the importance of the diagnosis to the individual will depend on the severity of the condition to which doctors are prepared to give the name. This has changed with time and the clinical diagnosis of asbestosis is now made more readily than it used to be some years ago.

The severity of asbestosis depends both on the amount of asbestos to which the individual has been exposed and the length of time since exposure first began. Asbestos fibres can remain in the lungs for long periods and the fibrosis that results from their presence continues to develop for many years after exposure stops. The development of asbestosis is, therefore, a slow process and even the gross dust exposures that used to occur in the past seldom led to sufficient fibrosis to cause death in less than 10 years. With reduction in the amount of exposure, the development of incapacitating fibrosis slows down and the reaction becomes so slight and its spread so slow that no person with otherwise healthy lungs would develop significant disability before reaching an age when he was likely to die of other causes. If, however, lung function is also affected by other causes, such as the development of chronic obstructive lung disease from tobacco smoke, the marginal effects of any additional fibrosis may aggravate symptoms and hasten the subject's death.

Lung cancer

The lung cancers that are caused by asbestos should properly be called bronchial carcinomas, as should the vast majority of lung cancers that are caused by other known agents. The term "lung cancer" is, however, in such general use that we shall continue to use it here.* Individual lung cancers that are caused by asbestos are, unfortunately, indistinguishable from those that are caused by cigarette smoking or by most of the other agents which, together with asbestos, are responsible for making lung cancer the commonest type of cancer to cause death in the population as a whole. Like other lung cancers, those that are caused by asbestos occur principally in the main bronchi; but they also occur in the smaller bronchi and in the periphery of the lung and they appear under the

Vervoon *et al* (1984) have obtained evidence which suggests that the

* Lung cancer properly includes a variety of other cancers that arise from parts of the lung other than the bronchial epithelium, such as the alveolar carcinomas that arise in the airsacs themselves and the sarcomas that arise from connective tissue. All tumours other than bronchial carcinoma are, however, extremely rare. None is known to be caused by asbestos and, for our present purposes, they can all be

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microscope in all the common histological forms (squamous carcinoma, small or oat-cell carcinoma, and adenocarcinoma).† Asbestos, moreover, seems to exert its effect synergistically with tobacco smoke, increasing the incidence rate among people of given age by the same proportion in smokers and non-smokers alike. Whether the two agents act to multiply each other's effect exactly is uncertain; but the interaction is so strong and so nearly multiplicative that, on present knowledge, we must assume that the chance that the lung cancer in a particular man or woman who has been exposed to asbestos is attributable in part to that exposure, is unaffected by his or her past smoking habits. This is convenient from a legal viewpoint, as it means that evidence about tobacco use is not needed and it may be extremely fortunate from the point of view of practical prevention; for the relationship presumably extends, to some extent at least, to ex-smokers as well. If so, analogy with the effects of stopping smoking in the general population would suggest that an individual, who has previously been exposed to asbestos and who currently smokes, can materially reduce the likelihood that the previous asbestos exposure will ultimately cause a lung cancer, simply by stopping smoking. In other words, cessation of smoking is likely to confer an even greater avoidance of risk of lung cancer in people with a history of heavy asbestos exposure than in the population at large.

Lung cancer attributable to asbestos, like carcinomas attributable to other known causes, does not generally occur until several years after the initial exposure. The first few cases in an exposed population may appear as soon as five to nine years after first exposure, but the excess risk of developing the disease continues to increase for a further 20 years and possibly for longer. Thus, no single "latent period" can be said to exist and the belief that it does has, on occasion, led to some seriously misleading predictions.

As with other environmentally induced cancers, the mean period from first exposure to the appearance of the disease is unrelated to the intensity of exposure, except in so far as heavy exposures shorten the expectation of life and consequently the time during which cancers can occur. We cannot, therefore, aim to reduce exposure to such an extent that the individual will inevitably die of something else before the disease is able to appear. Unless, unexpectedly, there turns out to be some threshold dose below which asbestos does not act as a carcinogen, all we can hope to do is to reduce the attributable risk* at each interval after first exposure to such a level that the balance of the risk and benefit associated with its use is socially acceptable.

† In some series asbestos-associated cancers have included an unusually high proportion of adenocarcinomas which are not normally found to be common in smokers (Kannerstein and Churg, 1972). This, however, may be due to the inclusion of a high proportion of cases examined at autopsy, when adenocarcinomas in the periphery of the lung are included, whereas they are frequently missed in series based on biopsies.

Mesothelioma

Mesotheliomas of the pleura or peritoneum are normally so rare, other than after occupational or other unusual exposure to asbestos, that any case that occurs after well attested and substantial asbestos exposure is commonly accepted as due to that exposure, subject only to the qualification that the time since the exposure occurred must be long enough to permit the disease to have been produced. This qualification is important as the delay between first exposure and effect is longer for mesotheliomas than for most other cancers; it is seldom less than 15 years, and possibly never less than 10 years. Any period less than 15 years must, therefore, throw doubt on the relationship of the disease to the exposure in question. As with lung cancer (and with other cancers due to other causes) increasing exposure increases the risk of developing the disease, but does not affect the length of the induction period. Periods of 30, 40, or even 50 years are common, and according to Peto *et al* (1982), who sought a model that would fit several of the largest sets of data, the risk continues to increase indefinitely with the time since exposure first occurred.

The relationship of mesothelioma to asbestos differs in several ways from the relationship for lung cancer. The hazard appears to be more strongly dependent on the type of asbestos and to be largely or wholly unaffected by smoking. As a result of these and other differences the ratio of the numbers of mesotheliomas and lung cancers produced by any given exposure to asbestos varies at least 10-fold from about 1-10 to 1-1 (see Chapters 4 and 6).

Other cancers

The evidence relating other types of cancer to asbestos is less clear and is discussed in detail in Chapter 3.

*We shall have occasion to refer to risk in this report many times. Unqualified, it means the chance that a particular event will occur in a given period. Qualified as attributable, it means the risk caused by a particular hazard, usually exposure to asbestos. The life-long risk is the chance that the event will occur before death can be expected from other causes. Relative risk is the ratio of the number of events observed in a special population to the number expected from the experience of some standard population with which it is compared; when used in this sense the period of time is understood to be the period of observation, unless otherwise defined.

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1 Origin and purpose of report

When, in September 1982, we were asked to undertake a further review of the adverse effects of asbestos on health, we had serious doubts about our ability to add anything worthwhile to the conclusions of the advisory committee that had been set up by the Health and Safety Commission (HSC) in 1976. That committee, whose terms of reference had been "to review the risks to health arising from exposure to asbestos or products containing asbestos ...." had reported to the Commission only three years earlier (Advisory Committee on Asbestos, 1979). Eventually, however, we were persuaded to undertake the review by the realisation that the quantitative relationships between the amount and type of asbestos to which individuals were exposed and the subsequent risks of developing diseases due to that exposure were still far from clear and that a study in which we had long been actively involved might, if developed further, provide data that would be of material assistance in resolving some of the doubts. We were, moreover, encouraged by the knowledge that Professor E D Acheson and Dr M J Gardner, who had previously written a report for the advisory committee on the medical effects of asbestos, had been asked to report on any further information that had subsequently been obtained which might suggest that any significant revision was required. This eased our task considerably and we are glad to acknowledge our debt, as so many others have done, to their lucid and wide-ranging reviews (Acheson and Gardner, 1979 and 1983). Dr Gardner also kindly provided us with an amended version of one of their Tables and, at his request, we have included this as an appendix to our report.

We have simplified our task by concentrating on those hazards that are liable to be met at work, as the evidence relating to non-occupational exposure is either too insubstantial to justify review or, if it is clear, is unquantifiable, as in the case of the household contacts of asbestos workers who developed mesotheliomas of the pleura from exposure to dust brought home on workers' clothes. We have, however, had an opportunity of seeing the results of the survey of airborne asbestos concentrations in different localities recently carried out by the Health and Safety Executive (HSE) for the Department of the Environment and we have, therefore, commented briefly on the implications of our findings for the assessment of the effects of non-occupational exposure as well.

In making our review, we have drawn heavily on the results of our own researches, carried out in conjunction with industrial medical officers and hygienists, on the mortality of men employed in an asbestos textile factory in Rochdale, and the relationships that we were able to observe between their rates of mortality and the amount of asbestos to which they had been exposed. These results will be published shortly in a scientific journal in the ordinary way (Peto *et al*, 1985). We have, however, also reported some of the details here, when they seemed necessary to explain our conclusions. In reviewing other data we have tried to avoid going over ground that has already been thoroughly explored, have referred to other reviews where necessary, and have concentrated on those aspects of the evidence which have been most in doubt and are the most important for the practical purposes of control. We have, therefore, summarised the medical effects of asbestos very briefly in Chapter 2 and have dealt with the following subjects at greater length in Chapters 3 to 5: (a) the types of cancer, other than lung cancer and mesothelioma, that can be produced in humans by inhalation of asbestos fibres; (b) the difficulties involved in assessing the quantitative effects of exposure; and (c) the quantitative evidence relating the intensity and duration of exposure to the effects observed.

The major report of the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario (1984) unfortunately appeared too late to influence our work to any great extent and our conclusions have, for the most part, been reached independently. We have, however, been able to make use of some new findings obtained by the Health and Safety Executive. We have referred above to the survey of airborne asbestos in the general environment. To this we have to add a review of asbestos fibre size distributions in different occupations that was made by Dr T C Ogden and the initial tabulations of the Health and Safety Executive's own mortality study of asbestos workers, which covered some 40 000 men and women who were employed in one or other branch of the industry between 1971 and October 1983. The initial tabulations refer to the data for over 31 000 men who were employed in England and Wales before the end of 1981, all of whom were examined individually on entry to the study. All these findings are to be published shortly and we are most grateful to the Executive and to the staff members who have carried out the various studies for permission to include references to them.

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3 Types of cancer produced

Cancers caused by asbestos

The evidence of an association between exposure to asbestos and the development of lung cancer and of mesotheliomas of the pleura and peritoneum has been reviewed frequently and is universally accepted as providing proof beyond reasonable doubt that asbestos is capable of causing all three diseases (see, for example, Acheson and Gardner, 1979; International Agency for Research on Cancer, 1977 and 1982). It will not, therefore, be examined further here.

The position with regard to other types of cancer is, however, very different. Suspicion that asbestos might cause gastro-intestinal cancer* was first raised by Selikoff, Churg, and Hammond (1964) in their report of the long-term follow-up of a small group of American insulation workers who had been employed for at least 20 years, and suggestions were subsequently made that asbestos might also cause several other types of neoplastic disease, including laryngeal, renal, and ovarian cancer and non-Hodgkin's lymphoma. There is, however, still some doubt about the interpretation of the evidence that has been produced. The International Agency for Research on Cancer (1977; 1982) seems to accept that the observed relationship with gastro-intestinal and laryngeal cancer is causal—although the wording is not clear—while the Advisory Committee on Asbestos (1979) and Acheson and Gardner (1983) accept that asbestos can cause laryngeal cancer and that it can probably also cause gastro-intestinal cancer, at least if the asbestos to which the individuals are exposed contains amphiboles.

Gastro-intestinal cancer

In the study reported by Selikoff, Churg, and Hammond (1964) 29 deaths were attributed to cancers of the oesophagus, stomach, colon, or rectum, whereas only 9.7 would have been expected on the basis of the US national age-specific rates over the same period. This difference was too great to be readily attributed to chance and, as the men had also suffered a grossly increased mortality from cancer of the lung and mesothelioma of the pleura and peritoneum and had been heavily exposed to asbestos dust (some of which must have been swallowed), it seemed reasonable to suggest that the asbestos was also responsible for the excess mortality from gastro-intestinal cancers as well. Similar results have not, however, been obtained in many other studies and, in their most recent report to the Health and Safety Commission, Acheson and Gardner (1983) commented that "large excesses [of alimentary tract cancer] continue in the studies where they were found in 1979, but in other studies there are no such excesses. The results remain inconsistent and leave open the question whether such an effect should be attributed to exposure *per se* or to some other factor(s) in the preparation and utilisation of asbestos in certain sectors of industry. In respect of cancers of the upper alimentary tract, social factors are particularly important, and differences between the workforces studied and the standard population with which they have been compared need to be taken into account."

The results of 18 studies in which standardised mortality ratios (SMRs) for lung, gastro-intestinal, and other cancers have been reported are listed in Table 3/1 and the data for men are shown graphically in Figures 3/1 and 3/2. When the expected numbers of gastro-intestinal cancers were less than 10 the results were combined in two groups, one for each sex. Studies are included in the tabulation only when the follow-up seemed reasonably complete and it was possible to separate the deaths attributed to mesothelioma from those attributed to other cancers or, in a few instances, when the most likely classification could be assumed. The numbers in Table 3/1 may not, therefore, agree exactly with the numbers in similar Tables published elsewhere. The data have also been restricted, whenever it was possible to do so, to those relating to periods at least 10 years after first employment, as such data are not diluted by observations made during periods when cancers attributable to occupation are unlikely to occur. It was not, unfortunately, always possible to use the same definition of gastro-intestinal cancer, as different investigators grouped their data in different ways. Sometimes "all digestive cancers" have been included, but whenever possible the data for gastro-intestinal cancers have been limited to cancers of the oesophagus, stomach, and colon and rectum.

The SMRs for lung cancer varied greatly from one study to another; but this was to be expected as the studies involved groups of workers who had been exposed under different conditions, some in mines, some in the manufacture of asbestos textiles, and some in the use of asbestos for insulation. Some, also, were exposed only to one type of fibre, while others were exposed to mixtures of two or more.

In all but one set of data, at least one mesothelioma occurred and, in the exceptional set, the SMR for lung cancer was significantly elevated. It must, therefore, be presumed that all the populations studied experienced some occupational hazard, and, with the two exceptions referred to below, all have been used to determine the correlation between the risks of lung, gastro-intestinal, and other types of cancer, despite the

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fact that in some of them the SMR for lung cancer was less than 1.00.*

First, the data for women have been omitted, as the relationship between the excess mortality from lung cancer and the mortality from mesothelioma is different in the two sexes and is likely to be different for the excess mortality from other cancers. Secondly, Selikoff, Churg, and Hammond's (1964) original observations (which are shown separately in the Figures) were omitted, as they had given rise to the hypothesis that asbestos caused gastro-intestinal cancer and should not form part of the data used to test it. The correlation between the SMRs for lung and gastro-intestinal cancer in the other studies is shown in Fig. 3/1. Despite the small numbers of expected cases and the necessarily large amount of random error in many of the series, the correlation is surprisingly close ($r = 0.916$, $P < 0.001$) and this supports the idea that, when the conditions of exposure are sufficient to cause an increased risk of lung cancer, they will cause an increase in the risk of gastro-intestinal cancer as well. The increase in the SMR for gastro-intestinal cancer is, however, generally much less than that for lung cancer and, if we postulate a linear relationship between the two sets of data, the excess mortality attributable to the former type of cancer, expressed as a proportion of the expected mortality in the absence of any special hazard, is only about 20% of the corresponding excess for the latter.

The correlation between lung and other cancers (apart from gastro-intestinal cancer) is shown in Fig. 3/2. It is again close ($r = 0.804$, $P < 0.001$) and the regression of the SMR for other cancers on the SMR for lung cancer indicates that the excess mortality attributable to other cancers is proportionally slightly less than that for cancers of the gastro-intestinal tract: that is, about 17% of the excess for cancer of the lung.

These findings can be explained in one of two ways: either occupational exposure to asbestos is a cause of cancer in practically every organ, or some of the deaths that are really due to lung cancer or mesothelioma are mis-certified as being due to cancer of some other type. Unfortunately the normal tests for an occupational hazard—the development of the disease after an appropriate time interval and positive relationships with duration and intensity of exposure—cannot differentiate between these two possibilities, as in both cases the excess mortality attributed to gastro-intestinal and to other cancers would have been occupational in origin.

Mis-certification of lung cancer often occurred in the past, before it was realised how common the disease had become, and it still does occasionally because the clinical presentation of lung cancer may mimic the presentation of many other types (presenting, for example, with abdominal ascites or an enlarged liver without any respiratory symptoms). Mis-certification of mesothelioma must have been even more common, for pleural mesothelioma was not even generally recognised as a specific type of cancer until 1960 (Wagner, Sleggs, and Marchand, 1960) while peritoneal mesothelioma was not generally recognised until after the conference on the biological effects of asbestos that was held in New York four years later (New York Academy of Sciences, 1965).

Two studies help to assess the effects that such mis-certification may have had. One was carried out in England by Newhouse and Wagner (1969), who sought information about the causes of death of 301 of the 436 ex-asbestos factory workers who had died in hospital or whose death had been the subject of an inquest or a coroner's post-mortem examination. Necropsy reports with histological examination (in 84 cases) or without (in 74 cases) were obtained for 158 subjects and these were personally reviewed. The results, which are summarised in Table 3/2, led to major changes in the numbers of deaths attributed to the different types of cancer, reducing, in particular, the gastro-intestinal cancers by half (from 14 to seven) and increasing the mesotheliomas fourfold (from five to 20). They are unlikely, however, to be typical of death certificate diagnoses in more recent years, when mesothelioma had come to be a recognised diagnosis.

In the second study, Selikoff, Hammond, and Seidman (1979) sought clinical and pathological evidence of the cause of death, as well as the certified cause of death, for all members of the asbestos workers' union in North America who were enrolled in their study on 1 January 1967 and who died within the following 10 years. Useful additional information was obtained for 71% of the 2,771 deaths, and this enabled the causes to be categorised in two ways: by the underlying cause on the death certificate and by the "best evidence" that the investigators had obtained. A detailed account of their methodology is given in Selikoff's (1982) report on "Disability compensation for asbestos-associated disease in the United States". The results are summarised in Table 3/3.

Interpretation of these observations is difficult, for three reasons. First the expected numbers of deaths were not obtained by means of a similar review, but from mortality recorded in the normal course of death certification, and this can give quite different results. For example, in one large autopsy series (which cannot, of course, be regarded as typical of all causes of death) Heasman and Lipworth (1966) found that 107 of the 253 deaths attributed to gastric cancer by clinicians were not confirmed at autopsy, while 86 gastric cancers found in the same series had not been so diagnosed during life. It is certainly justifiable to use the "best evidence" information to allocate properly all the deaths that were found to be due to cancers that are known to be produced by asbestos if the ordinary death certification shows that they were present in gross excess (that is, those due to pleural

* We have, throughout this report, expressed standardised mortality rates as the ratios of the numbers of deaths observed and expected, rather than in the more usual percentage form (ie 1.00 instead of 100). They are, therefore, identical with the estimated "relative risks".

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and peritoneal mesotheliomas or to lung cancer) but any further reallocation may serve chiefly to distort the comparison with the distribution of the expected deaths. It is doubtful, therefore, whether the changed ratios for cancers other than cancer of the lung that are shown in Table 3/3 under the heading of "best evidence" represent better estimates of the true ratios than those recorded on the basis of death certificate evidence. What is perhaps most striking about the results is that if we exclude cancer of the larynx (because it is part of the respiratory tract) and other unspecified cancers (which must have contained many cases of carcinomatosis due to lung cancer and peritoneal mesothelioma) we are left with 14 different types of cancer, only three of which have relative risks based on death certificate diagnoses of less than one. Moreover, the relative risk for the four types of tumour that arise from the lining of the gastro-intestinal tract (pharynx and buccal cavity, oesophagus, stomach, and colon and rectum) have almost the same relative risk (1.58) as the other ten (1.56).*

Secondly, it is not clear how intensively the clinical and pathological enquiries were pursued. On the basis of British experience of the reliability of death certificate diagnoses, it seems surprising that equally intensive enquiry of all deaths should have caused 37% (93/252) of those attributed to types of cancer that were not eventually regarded as asbestos related to be transferred into the asbestos related category (cancers of the oesophagus, stomach, colon–rectum, larynx, oropharynx or kidney), while none of the 670 cancer deaths that were originally in that category should have been transferred out. Even if all mesotheliomas are omitted, the contrast is still great: namely 39 out of 198 (20%) against none out of 554 (Selikoff, 1982).†

Thirdly, Selikoff *et al* (1979) used the US national rates to calculate the numbers of expected deaths, while the insultation workers, though scattered throughout the US and Canada, were wholly manual workers and are likely to have resided in the large towns. This cannot have accounted for much of the gross excess of deaths due to lung cancer, but it could have contributed materially to the smaller excess of some of the others.

The laboratory evidence weighs against the possibility that asbestos causes cancer in sites other than the lung, pleura, and peritoneum (which it may reach by retrograde spread from the pleura). Experiments on rats have shown that small proportions of ingested fibres reach the lymph stream (of the order of one ten-thousandth or less of the amount fed) including fibres of carcinogenic length (Sebastien, Masse, and Bignon, 1980). No such fibres were, however, found in any organ in a baboon after 1.6 g of mixed chrysotile and crocidolite was injected directly into the stomach (Hallenbeck *et al*, 1981). More importantly, asbestos has failed to produce gastro-intestinal or any other type of cancer in animals when given by mouth (Bolton *et al*, 1982; Condie, 1983).

Selikoff (1982) in his review, concludes that the excess of cancer of the pancreas in his own series of insulation workers was an artefact due to mis-certification, but that there were true excesses of cancers of the larynx, pharynx and buccal cavity, oesophagus, stomach, colon, rectum, and kidney that could be attributed to the men's occupation. The simplest explanation of the excess mortality of gastro-intestinal cancer, however, and in our opinion the most likely one, is that it results largely or wholly from misdiagnosis of cancer of the lung and mesothelioma of the pleura or peritoneum. We cannot, of course, rule out the possibility that asbestos may cause a small number of cancers in many different organs, even though there is no strong evidence that it does. In particular we do not wish to rule out the possibility that it may cause cancer of the oesophagus. The diagnosis is usually easy, misdiagnosis in place of cancer of the lung is rare, and in several studies the relative risk attributed to it is notably raised (Selikoff, Hammond, and Seidman, 1979; McDonald *et al*, 1980; Peto *et al*, 1985).

Initial tabulations from the Health and Safety Executive's national asbestos mortality study, which relate to the period 1971–81 when most doctors would have been alert to the possibility of the occurrence of mesothelioma in asbestos workers, give some support to our belief. The observations on men 10 or more years after first employment show that 34 deaths were attributable to mesothelioma, 153 deaths to lung cancer with a standardised mortality ratio of 1.35, and 44 deaths to cancers of the oesophagus, stomach, colon and rectum with a standardised mortality ratio of 0.71. If textile workers are excluded, to avoid any overlap with our own data (Peto *et al*, 1985), the figures are barely changed (mesothelioma deaths 34 and SMRs for lung and gastro-intestinal cancer 1.38 and 0.71).

Laryngeal cancer

The fibres that are capable of causing lung cancer pass through the larynx on their way to the lung, and may sometimes deposit on it. It would, therefore, seem reasonable that these fibres should also be capable of causing cancer of the larynx. In fact, however, the carcinogens that cause lung cancer on inhalation have not always been found to cause cancer of the larynx. Cigarette smoke certainly does, and so does mustard gas (though the evidence that the latter causes lung cancer is relatively weak) but arsenic, [illegible] chromium and nickel ores, and

* If cancers of the pancreas and liver are excluded, both of which are particularly likely to be misdiagnosed when there is a large true excess of lung cancer and peritoneal mesothelioma, there is some evidence of heterogeneity among the other 12 sites ($P=0.025$) but it is not marked.

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the combustion products of fossil fuels, which have given rise at times to gross hazards of lung cancer, have not yet been shown to cause cancer of the larynx.

Laryngeal cancer is relatively rare in men in most of the developed countries in which asbestos has been used, one case occurring for every 20 cases of lung cancer in the UK. Affected patients are, moreover, often cured, so that deaths attributed to it are few, and the disease is seldom listed separately in reports of the mortality of employees. Its rarity should make an occupational cause easy to recognise, if the disease were produced at all frequently (as was the case with the scrotal and nasal sinus cancers and angio-sarcomas of the liver that were induced by other occupational causes). The rarity of the disease, however, also makes it difficult to be sure that the risk of developing it is not increased as much as two or three times. The available data are summarised in Tables 3/4 and 3/5. The gross associations that were observed in the first two case-control studies (Stell and McGill, 1973; Shettigara and Morgan, 1975) cannot be due to chance and are so different from those observed subsequently that one must suspect that they were inflated by some aspect of the methodology employed.

Tobacco and alcohol are both major causes of laryngeal cancer and an excess of the order of 50% could possibly be due to above average consumption of either. We have, however, no reason to suppose that asbestos workers drink more than average and the survey carried out by the Health and Safety Executive at the start of its national asbestos mortality study (Carter, personal communication) suggests that, in Britain, the smoking habits of asbestos workers are unlikely to account for an excess of more than about 5%. Misdiagnosis of lung cancer and mesothelioma as laryngeal cancer is unlikely and could not, in any case, account for the findings in the case control studies summarised in Table 3/4. On the present evidence we conclude that asbestos should be regarded as one of the causes of laryngeal cancer. The risk following exposure relative to that in its absence is, however, less than that for lung cancer and the absolute risk attributable to asbestos is much less.

Other cancers

In their report to the Health and Safety Commission, Acheson and Gardner (1983) noted three studies in which an increased mortality from cancer of the ovary had been observed (Newhouse and Berry, 1979; Wignall and Fox, 1982; Acheson *et al*, 1982) in each of which the women had been heavily exposed to amphiboles and in each of which some women had developed peritoneal mesotheliomas. In two other studies no such increase in mortality was found (Acheson *et al*, 1982; Berry and Newhouse, 1983) but not peritoneal mesotheliomas were recorded, and in one of these other studies the women had been exposed solely to chrysotile. Two case-control studies covering 500 patients with ovarian cancer have failed to find any evidence of specific occupational exposure to asbestos (Newhouse *et al*, 1977; Booth, 1984) and it seems at least as likely that the positive findings are attributable to misdiagnosis of peritoneal tumours (which present clinically in a way that mimics very closely the occurrence of ovarian cancer with peritoneal spread) as that occupational exposure to asbestos had actually caused cancer of the ovary.

In their study of the mortality of insulation workers, Selikoff, Hammond, and Seidman (1979) concluded that the men had experienced an increased risk of renal cancer as a result of their employment, in addition to the risks of lung and gastro-intestinal cancer referred to above. Eighteen deaths were attributed to renal cancer against 8.1 expected, including 15 against 7.0 expected 20 years or more after first employment. Only two other studies have reported separately on this type of cancer. In one, Acheson *et al* (1984) observed two deaths against 1.4 expected in men making asbestos insulation board while, in the other, we observed one death against 4.29 expected in textile workers (or one against 2.72 expected 20 years or more after first employment; Peto *et al* (1985)). In the absence of any positive experimental evidence these data alone do not, in our opinion, justify the belief that asbestos can cause this type of disease.

A very rare type of cancer—large cell lymphoma of the oral cavity and gastro-intestinal tract—was also found to be related to occupational exposure to asbestos in a case-control study in California (Ross *et al*, 1982). Of the 28 affected patients, 17 had some evidence of substantial exposure against six of 28 controls matched for age, sex, and race, who were living in the same neighbourhood. This superficially surprising finding is given credence by the report of two deaths from lymphosarcoma of the small intestine in two small cohort studies of asbestos workers, which, like large cell lymphoma of the oral cavity and gastro-intestinal tract, is normally an extremely rare disease (see Ross *et al*, 1982 for references). The association is not supported by experience in Sweden (Bengsston *et al*, 1982; Olsson and Brandt, 1983) nor by Selikoff *et al*'s (1979) massive study of insulation workers in North America (Table 3/3), but the latter grouped all lymphomas together and large cell lymphomas limited primarily to the oral cavity and gastro-intestinal tract account for only about 5% of the total. On these data it is not now possible to reach any conclusion, but the possibility that these rare tumours can be produced by exposure to asbestos needs to be kept in mind.

Conclusions

We have divided this chapter into separate sections for different cancer sites, and we review here our overall conclusions:

(a) the marked correlation across studies between the relative risk for lung cancer and for all other sites combined is entirely explicable in terms of

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misdiagnosis of lung cancers and mesotheliomas. In particular, there are no grounds for believing that gastro-intestinal cancers in general are peculiarly likely to be caused by asbestos exposure. The increase in relative risk for gastro-intestinal sites is similar to that for other sites, and their selection for special attention appears to have been dictated largely by the findings in one study and the fact that they are common, so that a given observed relative risk may be statistically significant for these sites but not for others;

(b) if a small increase in relative risk is to be expected whether or not asbestos causes cancers other than lung cancer and mesothelioma, the fact that such increases are observed constitutes extremely weak evidence of a real effect. The strength of the evidence in relation to particular sites is therefore determined by the probability of misdiagnosis and the biological plausibility of the effect;

(c) we conclude that the evidence in relation to laryngeal cancer is quite strong. This is an unlikely site for misdiagnosed secondaries, the association is supported by case-control studies (in which diagnoses are usually reviewed), inhaled carcinogens are likely to be deposited in the larynx, and several lung carcinogens are known also to cause laryngeal cancer;

(d) we reserve judgment about the possibility that asbestos causes cancer of the oesophagus; and

(e) neither the epidemiological data so far published nor the biological evidence is sufficiently compelling to convince us that misdiagnosis or chance is not the simplest, and therefore most plausible, explanation of the effects observed for any other site. This conclusion would of course be weakened if further evidence indicated that substantial numbers of carcinogenic fibres reach certain organs, or if more impressive epidemiological evidence, such as the data on large-cell lymphomas of the oral cavity and gastro-intestinal tract, were reported and subsequently confirmed in further studies.

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Table 3/1 Standardised mortality ratios for cancers of lung, gastro-intestinal tract and other sites in asbestos workers (numbers of deaths in parentheses)

Sex	Type of exposure	Period of observation	Standardised mortality ratio for: lung cancer	gastro-intestinal cancer	other cancer	No. of mesotheliomas	Reference
M	Mining, chrysotile	1946–75[1]	1.03 (9)	1.03 (15)	0.94 (13)	1	Rubino *et al*, 1979
	" "	1951–75[2]	1.22 (224)	1.03 (209)	1.05 (317)	10	McDonald *et al*, 1980
	Manufacture, chrysotile[1]	1936–77	0.85 (28)	0.91 (18)	0.93 (26)	2	Thomas *et al*, 1982
	" "	1958–77[2]	2.00 (59)	1.46 (25)	1.28 (35)	1	McDonald *et al*, 1983a
	" " [4]	1958–77[3]	1.49 (84)	1.14 (59)	1.16 (70)	0	McDonald *et al*, 1984
	" " [5]	1953–83[3]	1.61 (113)	1.10 (47)	0.84 (48)	17	Peto *et al*, 1985
	" mixed	1941–79[3]	1.03 (143)	0.96 (103)	0.88 (77)	8	Berry and Newhouse, 1983
	" "	1947–80	1.96 (57)	1.11 (19)	1.00 (28)	5	Acheson *et al*, 1984
	" "	1944–76	1.72 (44)	1.04 (31)	0.95 (89)	3	Clemmesen and Hjalgrim-Jensen, 1981[6]
	" amosite	1941–73	6.29 (84)	2.07 (26)	1.62 (42)	11	Selikoff and Hammond, 1975
	Insulation, mixed	1943–62[3]	7.00 (42)	2.99 (29)	1.04 (17)	7	Selikoff *et al*, 1964
	" "	1967–76	4.24 (397)	1.67 (89)	1.98 (258)	102	" " , 1979
	" "	1933–75[3]	2.38 (103)	1.18 (40)	1.39 (38)	46	Newhouse and Berry, 1979
	Shipyards	1947–78	0.84 (84)	0.83 (68)	1.11 (87)	31	Rossiter and Coles, 1980
	Various	—	3.07 (55)	1.05 (16)	1.29 (36)	23	See footnote[5]
F	Manufacture mixed	1936–75	8.44 (27)	1.96 (20)	1.62 (33)	21	Newhouse and Berry, 1979
	" "	1941–79[3]	0.53 (6)	1.06 (29)	0.85 (51)	2	Berry and Newhouse, 1983
	Various	—	2.06 (27)	1.28 (15)	0.99 (90)	7	See footnote[6]

[1] Some little exposure to amphiboles, see Tables 4/1 and 4/3
[2] 20 or more years after first employment
[3] 10 or more years after first employment
[4] Cases of cancer and incidence ratios, not deaths
[5] Mancuso and Coulter (1963), Weiss (1977), Newhouse and Berry (1979), Finkelstein (1983)
[6] Mancuso and Coulter (1963), Acheson *et al*, (1982), Peto *et al*, (1985)

Table 3/2 Change in diagnosis of cause of death after reviewing necropsy data (*Newhouse & Wagner, 1969*)

	Cause of death	No. certified	No. removed	No. added	No. after revision
1	Cancer of lung	39	5	4 from category 6 2 " " 5 2 " " 7	42
2	Pleural mesothelioma	1	0	5 from category 1	6
3	Peritoneal mesothelioma	4	0	7 from category 4 3 " " 5	14
4	Gastro-intestinal cancer	14	7	0	7
5	Other cancer	14	5	0	9
6	Asbestosis without tumour	21	4	0	17
7	Other diseases	65	2	0	63
	All causes	158	23	23	158

Table 3/3 Observed and expected deaths among US asbestos insulation workers, by cause

Cause of death	Numbers of deaths observed		expected	Ratio observed / expected	
	DC*	BE*		DC*	BE*
Cancer of lung	429	486	105.6	4.06	4.60
Pleural mesothelioma	25	63	—	—	—
Peritoneal mesothelioma	24	112	—	—	—
Mesothelioma (not defined)	55	0	—	—	—
Cancer of larynx	9	11	4.7	1.91	2.34
Cancer of pharynx/buccal cavity	16	21	10.1	1.59	2.08
Cancer of oesophagus	18	18	7.1	2.53	2.53
" " stomach	18	22	14.2	1.26	1.54
" " colon/rectum	58	59	38.1	1.52	1.55
" " pancreas	49	23	17.5	2.81	1.32
" " liver	19	5	7.2	2.65	0.70
" " kidney	18	19	8.1	2.23	2.36
" " bladder	7	9	9.1	0.77	0.99
" " prostate	28	30	20.4	1.37	1.47
" " brain	17	14	10.4	1.63	1.35
" " testis	1	2	1.9	0.53	1.05
Leukaemia	15	15	13.1	1.15	1.15
Lymphoma	16	19	20.1	0.80	0.95
Skin	8	12	6.6	1.21	1.82
Other cancer	92	55	25.5	3.61	2.16
Non-infective pulmonary diseases	188	212	59.0	4.51	6.44
Other causes	1161	1064	1280.2	0.91	0.83
All causes	2271	2271	1658.9	1.37	1.37

After Selikoff (1982) and Selikoff, Hammond, & Seidman (1979)

*DC = cause according to death certificate
BE = cause according to best evidence

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Table 3/4 Risk of laryngeal cancer in asbestos workers: Case control studies

Reference	Country	Proportion of subjects exposed to asbestos: laryngeal cancer	Proportion of subjects exposed to asbestos: controls	Relative risk
Stell and McGill (1973)	England	31/100	3/100	14.5
Shettigara and Morgan (1975)	Canada	10/43	0/43	
Hinds, Thomas and O'Reilly (1979)	USA	25/47	19/47	1.7
Newhouse, Gregory, and Shannon (1980)	England	6/83	19/222	0.8
Burch *et al.* (1981)	Canada	14/184	9/184	1.6
Olsen and Sabroe (1984)	Denmark	17/326	34/1134	1.8

Table 3.5 Risk of laryngeal cancer in male asbestos workers: Cohort studies

Reference	Lung cancer relative risk	Larynx cancer: Number of cases observed	Larynx cancer: Number of cases expected	Larynx cancer: Relative risk
Mancuso and Coulter (1963)	2.8	1	0.4	2.5
Newhouse and Berry (1973)	4.3	2	0.4	5.0
[1] Rubino *et al* (1979)	1.0	4	1.5	2.7
[1] Selikoff *et al* (1979)	4.2	7	4.3	1.6
[1] McDonald *et al* (1980)	1.2[3]	16	15.0	1.1
Clemmesen and Hjalgrim-Jensen (1981)	1.6	6	2.9	2.1
[2] Berry and Newhouse (1983)	1.0	2	3.6	0.6
[1] Peto *et al.* (1985)	1.6	4	1.8	2.3
All cohorts	1.8	42	29.9	1.4

[1] 20 or more years after first employment
[2] 10 or more years after first employment
[3] Including an unknown number of pleural mesotheliomas
[4] Shown as 6 in one Table and 5 in another

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Fig. 3/1 Relationship between standardised mortality ratios for gastro-intestinal and lung cancer in male asbestos workers: ○ reported by Selikoff *et al* (1964), ● reported in other studies (see Table 3/1).

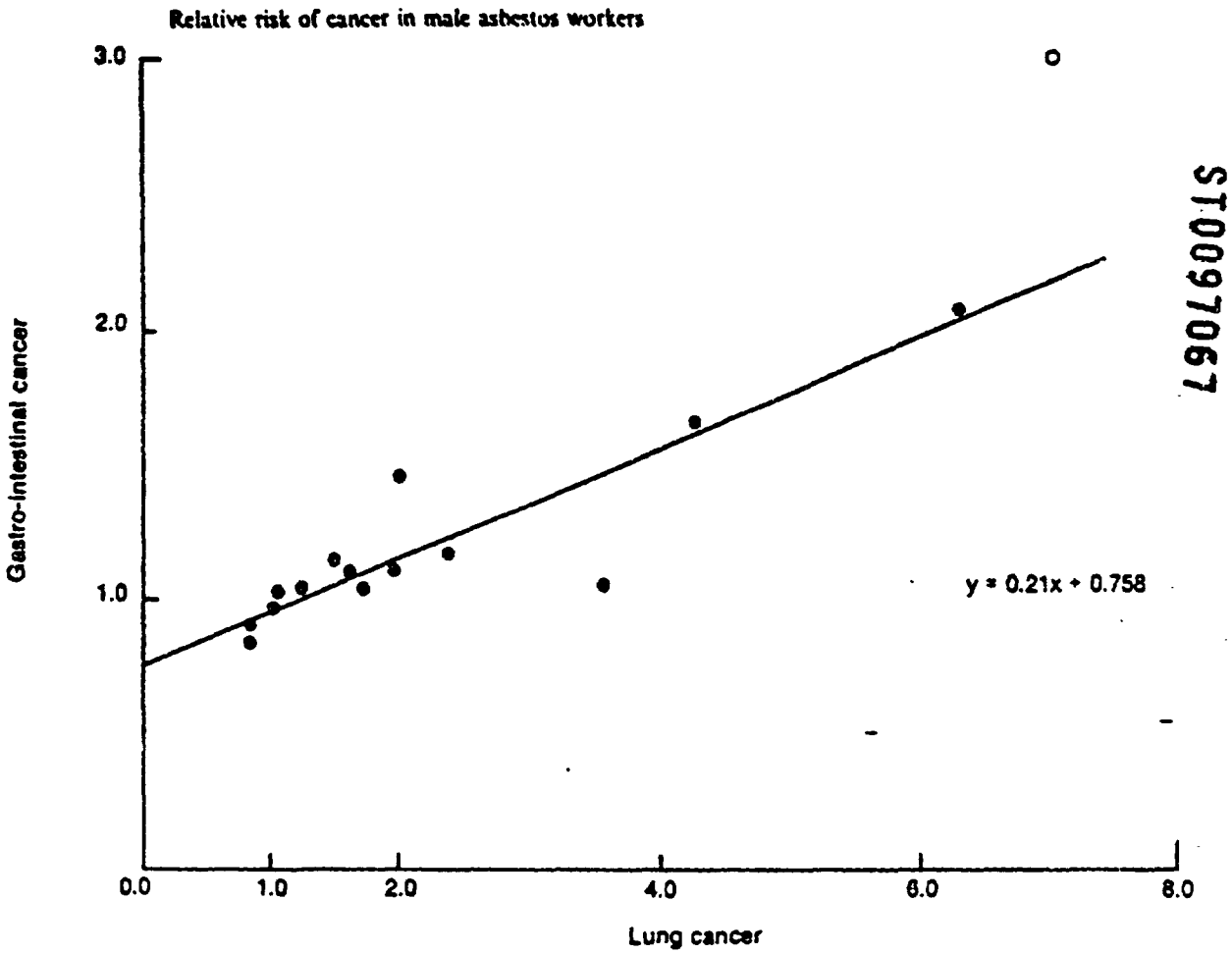

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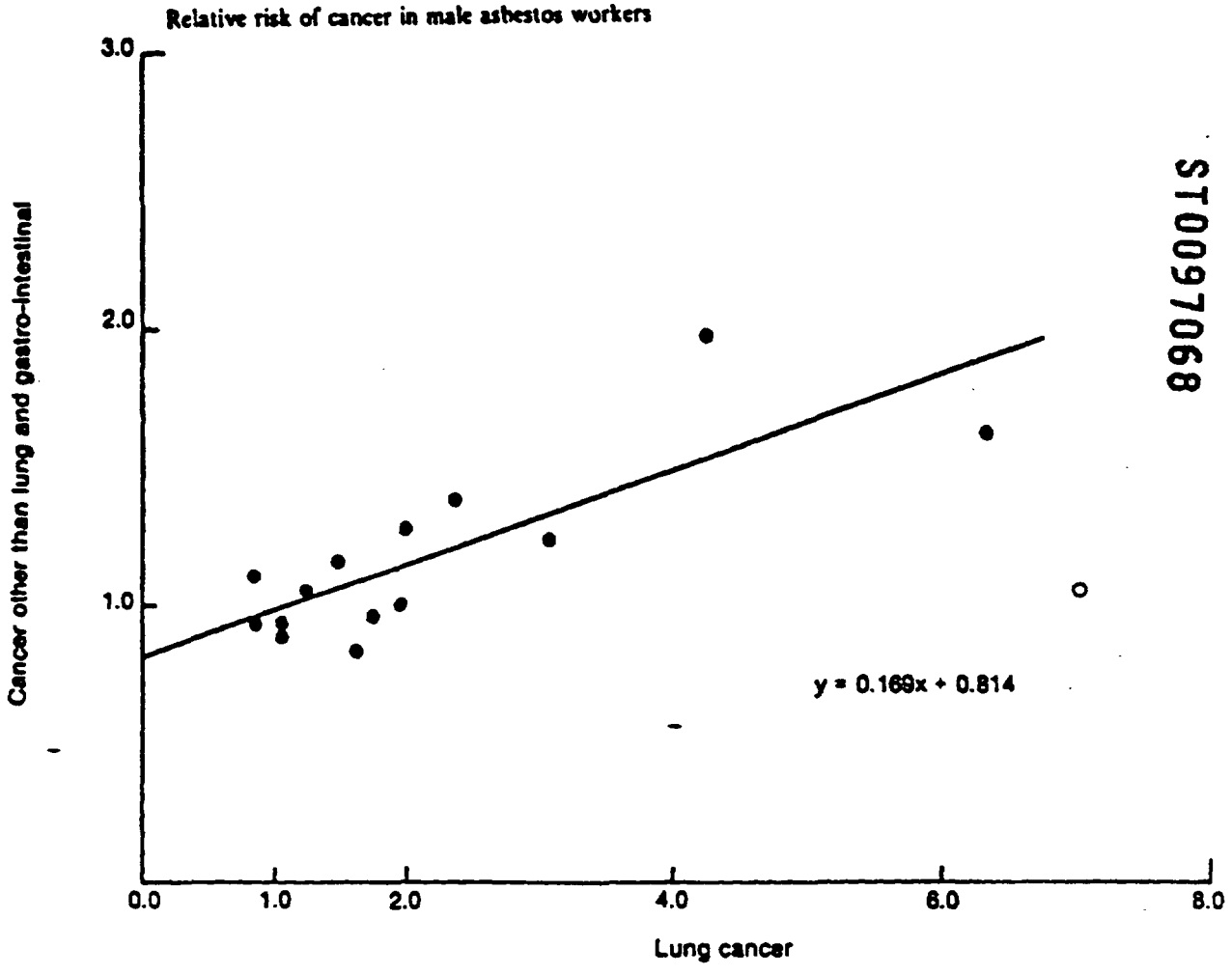
Fig. 3/2 Relationship between standardised mortality ratios for cancers other than lung or gastro-intestinal and lung cancer in male asbestos workers: ○ reported by Selikoff *et al* (1964), ● reported in other studies.



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4 Difficulties in assessing quantitative effects of asbestos

If it is difficult to decide how many types of cancer asbestos can produce, it is even more difficult to estimate the frequency with which asbestos will produce its different biological effects. This is due partly to the nature of the material, partly to the multitude of ways in which the material is used, and partly to the complexity of measuring the extent of both the relevant exposure and the biological response.

First, asbestos is not a single chemical but a family of compound chemicals that have crystallised in nature as long thin separable fibres with some useful mechanical properties in common. Secondly, the biological effects are due partly to the chemical constitution of the material and partly to the physical configuration of the fibres, both of which vary with the type of asbestos that is used. Thirdly, the proportion of fibres with specific configurations vary with the ways in which the material is handled; they are different in mines and mills, in factories producing different end products, and in places where the end products are used in different ways. Fourthly, asbestos is commonly mixed with other materials. For example, it constitutes only some 5–20% of the ore that is mined, but it is progressively refined during milling to produce commercial grades. These also vary, the textile grades having the longest fibres and greatest purity. During product manufacture other materials may also be added, as in making insulation board and asbestos cement. The presence of these materials may modify the effects of asbestos and increase the difficulty of assessing exposure.

It follows that the biological effects of exposure to asbestos cannot be predicted by simple measures of the amount in the environment, but require a detailed specification of the mineralogical type and the number of fibres of different sizes and shapes. This last is hardly characterised at all by weighing the amount of dust in the air or by counting particles of all types, and is characterised only imperfectly by most of the methods for counting fibres that have been used in the past. And to add to these difficulties, we have insufficient knowledge of the mechanisms of human carcinogenesis to know precisely what quantitative measures are most appropriate for measuring the biological response.

No major advance in our understanding of these problems has been made since the reports of the Advisory Committee on Asbestos (1979) and of Acheson and Gardner (1979, 1983) and we shall, therefore, summarise only the main facts that have to be taken into account in assessing the quantitative effects of occupational exposure. These are considered most conveniently under the heads of laboratory and epidemiological evidence and measures of exposure and response.

Laboratory evidence

The evidence relating to the physical characteristics of asbestos dust under different conditions of industrial use, its inhalation, deposition, and retention in the lungs, its biological activity in animals, and the correspondence (or lack of correspondence) between different methods for measuring the amounts of biologically active dust in the air was reviewed by Walton (1982) between the report of the Advisory Committee on Asbestos (1979) and Acheson and Gardner's (1983) second paper. Walton's review was undertaken under a contract with the Asbestos International Association to provide background information on methods for measuring airborne asbestos dust at the workplace that would be relevant to the development of regulations by the European Economic Community for the control of exposure, and was published in the Annals of Occupational Hygiene at the request of the Council of the British Occupational Hygiene Society. We have followed Walton in the way in which we have summarised the facts partly because of his experience in the field (he was engaged for over 30 years in studying the effects of respirable dust under the aegis of the National Coal Board and acted as World Health Organisation consultant to the US Department of Health, Education and Welfare on methods of dust measurement) and partly because he provides useful confirmation of the general conclusions of the other two reports.

Fibre size

Animal experiments show that the pathogenicity of asbestos dust correlates better with the number of long thin fibres than with the total mass to which the animals are exposed. The evidence suggests that the hazard from airborne asbestos is greatest from fibres of between five and 100 μm in length (above which they cease to be respirable), with diameters less than 1.5 or 2 μm, and with aspect ratios (that is ratios of length to diameter) of more than five to one. Very short fibres of 1–2 μm in length may not be carcinogenic at all (Wagner, personal communication) but there is no evidence of any cut-off point down to diameters of 0.05 to 0.1 μm or less. This last point is particularly disturbing as single asbestos fibres have diameters of about 0.02 μm and fibres less than about 0.2 μm cannot be detected by optical microscopes.

These conclusions are less precise than could be wished, partly because of the difficulties in determining the proportion of fibres of different sizes that were actually used in the experiments and partly because there are no sharp boundaries between hazardous and non-hazardous configurations. They are, moreover, mainly based on experiments in animals in which fibres were injected into the pleural or peritoneal spaces or were instilled intratracheally, and such conditions are far removed from the human situation.

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Moreover they refer directly only to pleural and peritoneal mesotheliomas and to pulmonary fibrosis. Inhalation experiments have confirmed that asbestos can produce lung tumours, but they have not used fibres closely graded by length and diameter, because of the extreme difficulty in preparing such materials in large enough amounts. The application of the conclusions with regard to lung tumours (most of which arise in humans in the large bronchi) must, therefore, introduce a further element of uncertainty.

Ideally different weighting factors should be given to fibres of different sizes, but this would be impossibly cumbersome and, in practice, we have to balance the exclusion of some fibres of marginal effect against over-estimation of the effect of other fibres that have been marginally included. In an attempt to do this, current regulatory standards have been based on optical counts of fibres defined as objects with lengths greater than 5 μm, diameter less than 3 μm, and aspect ratios greater than three to one. This is open to criticism not only on the basis of the biological evidence concerning hazardous sizes, but also because it results in many elongated fragments of other minerals (which may or may not be carcinogenic) being classified as fibres of asbestos (for review, see Walton, 1982). In the rest of this report we shall use fibre in its normal scientific sense and will refer to "regulated fibres" when we mean fibres as defined in the current regulations.

Fibre type

The four types of asbestos that have been used in industry to any material extent—the common chrysotile with its curly fibres and the three amphiboles (crocidolite, amosite, and anthophyllite) with their straight ones—all produce pulmonary fibrosis, cancer of the lung, and mesotheliomas of the pleura and peritoneum in animal experiments. Apart from showing this, such experiments have not been very helpful. No type has been shown to produce cancers of the gastro-intestinal tract or other non-respiratory cancers (other than peritoneal mesothelioma) and all types have produced fibrosis, lung tumours, and mesotheliomas with much the same frequency, when the effects of equal numbers of fibres are compared.

This was one of the few areas in which Walton (1982) and the Advisory Committee on Asbestos (1979) disagreed. The committee concluded that "using asbestos (prepared by hammer milling), which probably resembles more closely that used in the past by industry, similar respirable masses of chrysotile and amosite have been found to be less carcinogenic than crocidolite", while Walton concluded that "animal studies point to chrysotile being at least as damaging, and possibly more so, than crocidolite (or amosite) at equal respirable mass exposure concentrations and much more damaging for equal amounts retained in the lungs." Walton's interpretation of the evidence seems to us to be nearer the truth*, but the difference is unimportant as the quantitative differences in the effects produced were relatively small and the qualitative conclusion that all types produce the specified diseases with relative ease is over-riding.

Why this conclusion should be different from that drawn from epidemiological observations of humans, which is commonly thought to imply that chrysotile is less carcinogenic than amphibole asbestos, is not clear. The explanation may, perhaps, lie in the configuration of the curly fibres which make them more likely to be trapped in the upper air passages than the straight fibres or in the greater rapidity with which chrysotile is cleared from the lungs. This could be less important in rats that live for only two or three years than in humans in whom persistent fibres could have an opportunity of exerting an effect over several decades. But it may also be that pulmonary burdens have little relevance to the production of tumours in the bronchi.

Epidemiological evidence

Fibre size

Human evidence has little to contribute on the biological effects of fibres of different sizes, as human exposures have generally been to a wide range of sizes and environmental measures have seldom specified the mix with any precision. It seems likely, however, that the proportion of fibres of different sizes will vary with the origin and treatment of the asbestos, whether it is being mined or milled, and what it is being used for manufacture. More importantly perhaps the proportion of fibres that are detected by transmission electron microscopy, but are not visible with the ordinary optical microscope, may also vary. Published results based on transmission electron microscopy are few, complex, and difficult to compare (Dement and Harris, 1979; Hwang, 1983; Hwang and Gibbs, 1981; Rood and Streeter, 1984; Walton, 1982) and we are grateful to Dr T L Ogden of the Health and Safety Executive's staff for access to his recent review (Ogden, personal communication). This provides no

* Both Walton (1982) and the Advisory Committee reviewed the same evidence, and Walton suggests that the Advisory Committee might have come to different conclusions because they had followed the IARC (1977) in assuming that the experiments referred to by Reeves (1976), in which chrysotile produced less fibrosis than amosite or crocidolite and fewer cancers than crocidolite, were different from those that he had described previously (Reeves *et al* 1971; 1974). In his first reports, commercial grade samples of amosite, crocidolite, and chrysotile were said to have been ball-milled for 10 days and screened before they were disseminated with the aid of a hammer mill and fan system into large exposure chambers. The ball-milling was intended to reduce the fibre size, but unfortunately it also resulted in loss of the fibrous structure of the great majority of the particles and reduced the concentration of chrysotile fibres in the optical range to one-twentieth of the number of crocidolite fibres. In Reeves' last report, which reviewed the overall results of these experiments, reference to the preliminary ball milling was omitted.

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grounds for expecting a greater hazard from amphibole asbestos than from chrysotile. Some of the data suggest the possibility that the ratio of total pathogenic fibres to the number counted on optical microscopy may be somewhat greater when chrysotile is used for the manufacture of textiles than when it is used in the manufacture of friction materials and asbestos cement, and greater still than when chrysotile is mined but the differences are not consistent. If there are such differences this could go some way to account for the relatively high risks that have been reported for textile workers compared to other exposed groups in manufacture and mining (see Table 4/1).

Differences in the size of fibres produced in the crocidolite and amosite mines of the Transvaal and in the crocidolite mines of the Cape may also explain the relative rarity of the reports of mesothelioma in the Transvaal compared to the many reports of such cases in the Cape, as the fibres in the Transvaal mines tend to be thicker, to fall to the ground more quickly, and to be intercepted more easily in the upper air passages. Similar differences may also go a long way towards explaining the relative rarity of occupational cancer in the chrysotile mines of Quebec, where Hwang (1983) found that the proportion of fibres of putatively dangerous size, with lengths greater than 5 μm and diameters less than 2 μm, was a tenth of that in the crocidolite mines of the Cape (0.34% against 3.02%).

Fibre type

In contrast to the evidence on fibre size, human evidence has been extremely important in generating the idea that the amphiboles are more carcinogenic than chrysotile, particularly with respect to the production of mesotheliomas. The evidence is not, however, as clear as one would like. Observations have been made in different countries and over different periods, and the results have been presented in different ways. It is, therefore, extremely difficult to make the precise comparisons that are scientifically desirable.

The results of 22 cohort studies of 30 populations which are presented in ways that enable reasonable comparisons to be made between them, are summarised in Tables 4/1 to 4/3. The great majority were listed in Acheson and Gardner's (1983) Table 3. Not all the figures are, however, the same, partly because Acheson and Gardner provided us with a list of amendments (see Appendix) and partly because we chose to select groups of results that seemed more appropriate for our present purpose. For example, we divided the data reported by Thomas *et al* (1982) into two parts, to show separately the observations on men exposed only to chrysotile and those on the few men who were also exposed to amphibole asbestos; and we used, whenever practicable, observations relating to periods 20 or more years after first employment, when asbestos-induced cancer is most likely to occur. We also excluded studies that did not permit the [illegible] mesotheliomas from ideal. Some of the observations covered periods before mesotheliomas—and particularly peritoneal mesotheliomas—were widely recognised as specific entities, and even the later observations that were made when attention had been focused on the possible occurrence of the disease, are likely to have overlooked some individual cases.

A further difficulty in interpreting Tables 4/1 to 4/3 is the great variation in lung cancer rates between these different populations. Asbestos acts synergistically with smoking in causing lung cancer, but not in causing mesothelioma, and a disproportionately low ratio of excess of lung cancer to mesothelioma is therefore to be expected among workers who smoke less. Women smoked very much less than men in the past, and their ratio of excess lung cancer to mesothelioma would therefore be expected to be considerably lower than among men; but there have also been marked changes over time and substantial differences between different countries in male lung cancer rates, all of which must have had some effect on the observations.

The Tables show separately the observations that have been made for men and women exposed: (i) only to chrysotile; (ii) mainly to chrysotile (that is, employees in industries in which chrysotile is believed to have constituted at least 95% of the total asbestos used); (iii) only to crocidolite or amosite; and (iv) to mixtures of fibre types that include both chrysotile and substantial amounts of amphiboles, or to types that have not been defined. The second category is divided to show separately observations made in (a) factories where amphiboles were not introduced until the early 1950s or later, and (b) factories where small amounts of amphiboles had been used for much longer. In group (a) very few mesotheliomas could be due to amphibole asbestos as the time since first exposure will not have been long enough for many cases to occur during the periods under observation. Within each Table, the observations are also shown separately for different types of industry such as mining and milling, the manufacture of textiles, cement, friction products etc, insulation work generally, and work in shipyards.

Each entry shows the total number of deaths to indicate the size of the study, the number by which the lung cancer deaths exceeded the number expected and the corresponding ratio of the numbers observed and expected, and the total numbers of pleural and peritoneal mesotheliomas diagnosed irrespective of the cause to which death was attributed on the death certificate. It is not, unfortunately, possible to place much reliance on the excess number of lung cancer deaths when the ratio of observed to expected deaths is low, as its value depends crucially on the suitability of the standard population chosen for comparison. In many cases this has been the country as a whole and this may not be appropriate for industrial employees in the area in which the particular men and women worked.* Unless local rates are used, or the use of

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national mortality rates has been validated, mortality ratios of anything under 1.5 may be largely or wholly artefacts. Equally, of course, small relative risks may be underestimated or missed entirely if the normal risk in the area in which the factory is located is below the national average.

Tables 4/4 and 4/5 summarise the data for exposure to different types and, despite the qualifications made above, it seems clear that there are important differences between the groups. Exposure that was solely or principally to chrysotile led to fewer lung cancers in proportion to the total number of deaths, fewer mesotheliomas, and a smaller proportion of mesotheliomas arising from the peritoneum. Indeed, it may even be doubted whether chrysotile is capable of producing peritoneal mesotheliomas.

No peritoneal mesotheliomas are recorded in Tables 4/1 and 4/4 as having arisen from exposure to pure chrysotile, and although two cases have been described elsewhere, there is reasonable doubt about both. One peritoneal tumour was referred to by Acheson and Gardner (1983) as having occurred in men exposed only to chrysotile in the manufacture of asbestos textiles (then referred to as McDonald *et al*, unpublished a., now as McDonald *et al*, 1983a). A small amount (less than a tonne) of crocidolite yarn was, however, used in the factory each year between 1950 and 1972 to unite woven tape and braided packing and some exposure to crocidolite cannot be excluded, as the affected man had worked in the plant from 1925 to 1965.* We have classed the workers in this plant as having been exposed mainly to chrysotile. Another case appears to be included in Acheson and Gardner's (1983) Table 3, but it is clear from the text that they recognised that the series in which it occurred (Dement *et al*, 1982) was included in the larger series referred to above. A second possible case was described by McDonald (1980) in his review of all the mesotheliomas that occurred in Quebec between 1960 and 1978. Sixteen mesotheliomas were found to have occurred in miners who were not also known to have worked in a factory that used crocidolite, but the one man to have a peritoneal tumour (combined, as it happened, with a pleural tumour) was one of the two who could have been exposed to crocidolite in the factory that processed crocidolite for the manufacture of gasmasks for a short period.

That chrysotile can cause pleural mesothelioma would seem to be settled by the observation of at least 14 cases in Quebec miners and millers. Some of the affected men may have been exposed to amphiboles elsewhere, but the majority probably were not and, if the tumours were diagnosed correctly† the causal nature of the association can be questioned only on the grounds that Quebec chrysotile contains a small amount (on average less than 1%) of tremolite, an amphibole whose biological effects may be similar to those of crocidolite. Interest in the effects of tremolite has been raised only recently, but it is clear that some samples are powerful inducers of pleural mesothelioma while others are not. As with other asbestos fibres the differences seem to be due to the physical configuration of the fibres, very short fibres not having any effect (Wagner, Chamberlain, *et al*, 1982). On present knowledge, we cannot express any opinion on the likely contribution of tremolite to the production of cancer in the Quebec miners, but it should be noted that Pooley (1976) found the mineral in the lungs of miners in association with pulmonary fibrosis and pleural plaques, but saw no correlation with the presence of mesotheliomas. It is not practicable to remove tremolite from chrysotile for commercial purposes and any distinction between the effects of chrysotile and tremolite may, therefore, be considered academic, unless supplies of chrysotile can be obtained in which little or no tremolite is present.*

The pathological evidence is not very helpful. The finding that chrysotile fibres, including long ones of carcinogenic size, were present in much greater numbers in the pleura than amphibole fibres, despite the fact that amphiboles were more often present in the lung (Sebastien, Janson, *et al*, 1980) suggests that it might. Other studies, however, have shown that the asbestos fibres in the lungs of subjects who develop mesotheliomas are mostly amphiboles, even when they have been exposed principally to chrysotile. Berry and Newhouse (1983) for example, compared the histories of the jobs undertaken within a factory manufacturing friction materials by the 10 men and women who developed pleural mesotheliomas with those given by 40 control employees matched for sex, age, and date of starting work in the same factory, who were still alive when the affected men and women died. The results showed a strong association between the development of mesothelioma and exposure to crocidolite, but their interpretation was complicated by confounding between exposure to crocidolite and particularly heavy exposure to chrysotile. The numbers were small, and when the confounding was taken into account the differences were not statistically marked (P, two-tailed, = 0.06).† It is notable, however, that there was evidence to suggest that the two men and women with mesotheliomas who were not known to have had any exposure to crocidolite when they were under observation in the factory may have been exposed to it at other times.

*A very small amount of amosite was used experimentally in carding in the late 1950s, but this seems less likely to be relevant as the affected man died in 1967 and an induction period of 10 years would be unusually short.

†According to McDonald (personal communication) one of the diagnoses was disproved at autopsy and two diagnoses that were made only in life were dubious. Several of the other cases occurred in men who were employed at a time when crocidolite was being used locally in a factory and mill.

*The amount of tremolite observed in samples from different areas and from different mines within an area has varied from 0 to 5%, but it is not known whether it would be possible to obtain supplies in which the level of contamination was consistently lower than it has been in the past.

†Even this adjusted significance level may be exaggerated as adjustment for a confounding factor by dichotomising is frequently inadequate.

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Pathological observations at autopsy are unlikely to settle the question, as chrysotile fibres seem to be removed from the lungs so much more readily than fibres of other types (Rowlands *et al*, 1982). Large scale studies in North America (McDonald, McDonald, and Pooley, 1982) and in the UK (Wagner, Pooley, *et al*, 1982) have even failed to find an excess of chrysotile in the lungs of men and women dying of mesothelioma or (in the UK) of asbestos-induced disease of any type in comparison with that in the lungs of unaffected controls, as is illustrated by the data in Table 4/6. We must, therefore, assume either that chrysotile is practically harmless—which is patently untrue—or that it initiates disease and is then largely removed. One glimmer of light may be provided by the finding referred to previously (Sebastien, Janson, *et al*, 1980) that chrysotile persists in the pleura, and more observations of the amount of each of the different types of asbestos that can be found in this site in people heavily exposed to asbestos might help to clarify the position.

The data summarised in Table 4/4 suggest that male asbestos workers exposed principally or exclusively to crocidolite suffer a mesothelioma risk of the same order as their excess lung cancer risk, whereas exposure to amosite or chrysotile causes many more lung cancers than mesotheliomas. This inference is less certain than these data suggest at first sight, as only two cohorts of men exposed largely or exclusively to crocidolite are included, and the data on women are difficult to interpret because of their relatively low smoking rates. In spite of these reservations, however, we conclude that the most plausible interpretation of the available data is that crocidolite causes a disproportionately high mesothelioma incidence.

This conclusion is supported by the association between crocidolite exposure and mesothelioma observed by Berry and Newhouse (1983), the comparison of asbestos textile workers exposed almost exclusively to chrysotile (McDonald *et al*, 1983a) with men working in a similar environment who were also exposed to crocidolite (McDonald *et al*, 1983b), the relatively high mesothelioma incidence in the Rochdale factory, where there was also some long term exposure to crocidolite (Peto *et al*, 1985) and the anecdotal and clinical experience of men and women exposed to crocidolite dust in and around the South African mines.* In calculating dose-specific mesothelioma risks for pure chrysotile exposure, we have therefore assumed that a proportion of the mesotheliomas in the Rochdale cohort were caused by crocidolite (see Chapter 5). In our opinion the epidemiological data summarised in Tables 4/4 and 4/5 show that chrysotile can cause both mesothelioma and lung cancer, but both the proportion of deaths attributed to mesothelioma and the ratio of the number of mesotheliomas to the excess number of lung cancer deaths are lower when exposure has been limited or almost limited to chrysotile. The mesotheliomas certainly due to chrysotile alone are, moreover, all pleural, and there is no compelling evidence that chrysotile can cause mesotheliomas of the peritoneum. The position with regard to amosite is less clear. Amosite certainly causes both pleural and peritoneal mesotheliomas, and it therefore seems likely that it is more dangerous than chrysotile; but the overall ratio of mesothelioma to excess lung cancer caused by amosite appears to be substantially lower than that caused by crocidolite, and the pooled data shown in Table 4/4 suggest that this ratio may not be much higher for amosite than for chrysotile alone.

How the lung cancer hazard compares quantitatively when both types of asbestos are used for the same purpose is more difficult to decide. Superficial examination of Table 4/5 suggests that the hazard from chrysotile is less. The results are not, however, standardised for the type of industrial process nor for such biological factors as length of employment or time since first exposure. The last might be expected to have biased the results slightly against chrysotile as the proportions of deaths that were recorded in studies that excluded observations less than 20 years or more after first employment were 87% for men and women exposed solely to chrysotile, 100% for those exposed mainly to chrysotile but with some late exposure to amphiboles, 24% for similar men with some early exposure to amphiboles, 53% for those exposed to substantial mixtures of both chrysotile and amphiboles, and 0% for men and women exposed solely or mainly to amphiboles. A proper comparison is not possible, however, as the various authors have not published their results in sufficient detail. It is difficult, too, to allow for the effects of the different industrial processes. Many of the men who were exposed only to chrysotile were employed in mining and milling and there is reason to think that the mining of chrysotile may involve less hazard than its manufacture or its use in insulation. It is notable also that half the deaths of those who were exposed principally to chrysotile occurred in men and women who were engaged in the manufacture of friction products compared to none in those who were exposed to any large amount of amphibole asbestos and it seems, from comparisons within Tables 4/1 and 4/3, that the risk of this industrial process has been less than from the manufacture of textiles and the use of asbestos for insulation. Only one type of work has permitted a direct comparison between the risks of chrysotile and crocidolite when they are both used for the same purpose: namely, the manufacture of gasmasks during the second world war. The numbers are small, but the evidence that has been obtained by Jones, Smith *et al* (1980), McDonald and McDonald (1978), and Acheson *et al* (1984) is impressive, and we have no hesitation in concluding that, used for this purpose the hazard of cancer from chrysotile is

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crocidolite is more hazardous than chrysotile when both are mined (Hobbs *et al*, 1980; Armstrong, personal communication). It does not, however, necessarily follow that the hazard is less for the same fibre count, for which no data exist for crocidolite.

Associated agents

A further complication is that other materials that are used in conjunction with asbestos in some of the manufacturing processes may also have biological effects on the lungs which may modify the effects of asbestos. This could be relevant to the production of peritoneal mesotheliomas, as these have been most frequent in the manufacture and use of insulation materials in which sodium and calcium silicates have commonly been used as fillers. Browne and Smither (1983), for example, have suggested that such other dusts may help to block the normal lymphatic drainage from the lung and so encourage retrograde drainage from the pleural to the peritoneal cavity (Becklake, 1976).

Measures of exposure

A crucial element in any attempt to estimate the quantitative effect of exposure to a given amount of asbestos dust is the reliability of the methods that have been used for measuring exposure in the past. All who have examined the question have drawn attention to the weakness of the available data. They have, however, implicitly concluded that the recorded measurements were sufficiently robust to justify making the simple assumptions about them that are needed to estimate a relationship between dose and effect. This conclusion is so critical that we have thought it essential to re-examine the background to it.

In brief, very few measurements of any kind exist for the time before 1950, when exposures were more (and sometimes much more) intense than they are now, and which gave rise to the majority of the high mortality rates that have been observed. Moreover, these early measurements were of the concentration of particles of all kinds (following the practice of other industries) and only a small proportion of the particles observed were fibres.* Since then a variety of instruments have been used which have quantified exposures in different units mostly aimed at providing a more specific measure of the dangerous fibres, and conversion factors have had to be derived to enable the various sets of results to be used to predict the effect of exposure to concentrations of dust measured by modern methods.

The main variations in the methods of measurement that were used in the Rochdale textile works which we have studied (Peto *et al*, 1985) have been as shown in the accompanying table.

Both the LRTP and the RPC can provide counts equivalent to those obtained with a membrane filter sampler. The RPC, however, counts particles as well as fibres, and is calibrated against the membrane filter sampler under fixed conditions. In certain areas parallel RPC and membrane filter results correlated so poorly that the RPC was not routinely used. Since 1975, personal sampling with the instrument attached to the worker's coat has increasingly been substituted for static background sampling and this has introduced a further difference.

Elsewhere in Britain, similar changes have taken place, though their timing and the types of instrument used have varied. The Owens jet impinger instrument was used widely to count dust particles before the Asbestos

Period	*Instrument*	*Method of evaluation*	*Parameter*	*Unit†*
1951–60	Casella thermal precipitator (CTP)	Incinerated, × 1000 dark field	Particles (including fibres)	p.ml^{-1}
1961–64	Oatway long running thermal precipitator (LRTP)	not incinerated, × 500 light field	Fibres >5 μm long, ratio length to diameter >3:1	f.ml^{-1}
1965–74	Membrane filter sampler	× 500 phase contrast, full field	"	"
	or Royco automatic particle counter (RPC)	automatic	"	"
1975 to date	Membrane filter sampler	× 600 phase contrast, graticule grid count	"	"

† Particles were counted in Rochdale down to a diameter of 0.5 μm; 35 particles per ml are equivalent to one million particles per cubic foot (mppcf), the unit routinely used in North America.
f.ml^{-1} = fibres (as defined by regulations) per ml.

* Ayer and Lynch (1967) for example, found more than 90% motes (non-fibres) in US impinger samples taken in "asbestos textile plants where the only dust generated comes from asbestos".

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Research Council (1968) issued its guidance notes on counting, and other impingers were used in the US until they were superseded by membrane filter samplers or automatic particle counters that could be calibrated to give an approximate fibre count.

Before 1950 very few measurements were made, and the amount of airborne asbestos dust in workplaces in the 1930s and 1940s can be compared with that in the 1950s only by the subjective judgment of individuals with experience of both (or, perhaps more reliably, by comparing the mortality of pre- and post-war asbestos workers).

Data collected in the form of millions of particles per cubic foot or particles per ml have to be converted somehow to regulated fibres per ml. Unfortunately it has become clear that no simple conversion is possible or is to be expected. Fibre counts ranging from about 3% to more than 50% of the particle counts have been obtained for different processes (mining and milling and manufacture of textiles, friction materials, and asbestos cement) while no comparable counts at all are available for the important class of exposure from the use of asbestos in insulation. Even worse, a similar range of variation has been obtained for areas within a single plant (Steel, 1979; Walton, 1982; Acheson and Gardner, 1983). Moreover, when counts have been made simultaneously by different methods, the correlations obtained have invariably been weak (of the order of 0.3 to 0.6) and the relationships between particles and regulated fibres have not always been linear. Dagbert (1976), using the massive data obtained by Gibbs and La Chance in the mines and mills of Quebec, found it necessary to transform the counts to logarithms before a linear relationship between them could be obtained. The relationship so obtained gave conversion factors which, according to Steel (1979) fell from 23.0 to 11.0 as the particle counts rose from 0.1 to 1.0 million per cubic foot.*

What Steel (1979) did not mention was the enormous variation in the relationship between the counts on which Dagbert's formula was based. This variation was, in fact, so great that the 95% confidence limits attached to the formula allowed for a hundred-fold difference in the conversion factors deduced from it. According to Dagbert the 95% confidence limits of the conversion factors appropriate for three typical particle counts were approximately as follows:

mppcf	*factor to convert to f.ml^{-1}*
0.1	1.2 to 116
1.0	0.6 to 58
10.0	0.3 to 27

The results of 623 parallel measurements made by the two methods in seven mines showed a low overall correlation (Fig. 4/1; r = 0.50). There was, however, wide variation both between mines and between processes within mines. For one mine, the overall correlation was 0.93, while for the other six it varied between 0.34 and 0.61 (Dagbert, 1976). The results for the process of "fibre screening", which gave one of the higher overall correlations (r = 0.75), are shown for different mines in Fig. 4/2. There are only 10 pairs of samples in each mine, but the results suggest that there may be quite a high correlation in some mines and virtually none in others. Differences are very much larger between than within mines. Measurements were consistently low for both fibres and particles in mines 24* and 29 and high in mines 22 and 28, and the high correlation may therefore be an artefact produced by variation in the average level in different mines.

The analysis of the results of comparative measurements made simultaneously at the Rochdale textile works in 1977, which were reported by the Committee on Asbestos of the British Occupational Hygiene Society (1983), led to the conclusion that, using the graticule grid method referred to below, membrane filter fibre counts were related to particle counts obtained by the Casella thermal precipitator by the formula,†

$$f.ml^{-1} = 0.071 \text{ particle count } ml^{-1} + 0.6$$

This formula was, however, derived only after using a statistical technique to reject in turn a number of outlying points that depart significantly from a linear relationship, which eliminated nearly all the observations of particle counts greater than 100 ml^{-1} (2.86 mppcf). Most of the rejected points were among the first to be produced and the observations were interfered with by a "bloom" that formed when the glass collecting slides were heated to burn off smoke particles. This was particularly unfortunate as the pre-1961 counts, when the Casella thermal precipitator was used, were regularly above 100 ml^{-1}. The detailed data have been made available to us by Sykes (1984) and re-analysis shows very little correlation for the

* Dagbert's formula is cited by Steel (1979) as:

$$mppcf = 10.97\ (f.ml^{-1})^{0.44},$$

where mppfc stands for million particles per cubic foot measured by the impinger and f stands for regulated fibres measured by the membrane filter. This would, in fact, give conversion factors which increase with increasing particle counts instead of falling. Reference to Dagbert's (1976) original article shows that the formula was cited incorrectly and should have been:

$$f.ml^{-1} = 10.97\ (mppfc)^{0.44}$$

The conversion factors cited by Steel (1979) and referred to above

* The code numbers are those given to the mines by Dagbert (1976).

† Particle counts expressed in terms of mppcf are approximately converted to particle counts per ml by multiplying by 35. A printing error caused the formula to appear incorrectly in Steel (1979) as 0.71 particle count ml^{-1}. Elsewhere in our report we have tended to record particle counts in terms of mppcf, because of their approximate equivalence to the initial regulated fibre counts per ml at Rochdale (see p. 18).

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observations on counts above 100 particles ml^{-1} ($r = 0.083$, $P > 0.1$) and a materially different regression formula if all observations are included:

$f.ml^{-1} = 0.031$ particle count $ml^{-1} + 1.90$

Many reservations were attached to the use of the first formula by the British Occupational Hygiene Society's (1983) committee, and neither formula can be accepted as valid for higher levels of pollution or for other factories or mines in which asbestos was processed in a different way.

Unfortunately there was no period of overlap at Rochdale when particles and fibres were counted routinely, so that comparison between the results of the two methods, when in normal use, can be made only by comparing the results obtained in the same parts of the factory averaged over the years 1960 and 1961. The British Occupational Hygiene Society (1968; 1983) made this comparison in the course of their study of the effects of asbestos on lung function, and concluded that the conversion factor (mppcf to $f.ml^{-1}$) was approximately one. We have re-examined the data and show the results in Fig. 4/3. A central estimate of the conversion factor from mppcf to $f.ml^{-1}$ is certainly not far from one* but the scatter is too wide for much confidence to be placed in it. One extreme point is largely responsible for the size of the correlation coefficient and if this point is omitted the coefficient is halved (from 0.665, $P < 0.01$ to 0.334, $P > 0.1$).

A further difficulty that has not so far been taken into consideration, and has generally been overlooked, is that the particle counts have frequently been made with different instruments. The methods used to recover particles from the air and prepare them for counting are entirely different when counts are made with the Midget Impinger, which was used in North America, and the Casella Thermal Precipitator, which was most commonly used in Britain and throughout the relevant period in Rochdale. With the Midget Impinger counts were made at low magnification (× 100) in liquid as opposed to air, which reduces visibility, and particles were collected efficiently only down to about 0.8 μm diameter. Much smaller particles were collected and made visible by the thermal precipitator, though very small particles (less than 0.5 μm diameter) were not counted. No parallel counts with the two instruments were made, but it is only to be expected that the factors used to convert particle counts to regulated fibre counts will be different when the particle counts were made in such different ways. The effect of these differences on the estimate of the dose response relationship is discussed on p. 36.

The two other developments that have complicated comparison of current levels of pollution with those measured in the past are the introduction of the graticule grid method of counting fibres and the substitution of personal sampling for static background sampling of selected areas. The former is a refinement that has certainly helped to reduce intra and interobserver errors in counting, but not all observers undercounted using the old full field method (British Occupational Hygiene Society, 1983) and the arbitrary multiplication of pre-1977 regulated fibre counts by two to bring them into line with modern methods may be appropriate for some sets of data, but is not necessarily so for all. Skidmore and Dufficy (1983), for example, suggest a factor of under 1.2.

The latter, which requires measurements to be made by an instrument attached to the coat lapel of an individual worker, has sometimes been regarded as again approximately doubling the counts, but it is far from clear that this is a proper generalisation. Steel (1979), in the Advisory Committee's report, accepted a factor of two as representative, but pointed out that the factor could vary from about one to 10. In areas where static measurements (and hence, ambient levels in the building) are less than about 1 $f.ml^{-1}$, personal measurements have usually been found to be considerably higher than the static figures, perhaps because occasional work practices or proximity to emission sources make a substantial contribution, in such circumstances, to the total inhaled dose. The few observations for which the static measurements exceeded about 1.5 $f.ml^{-1}$ have, however, shown no clear tendency for the corresponding personal measurements to be higher, as is shown in Figures 3–6 of Appendix 2 to the British Occupational Hygiene Society's (1983) report.

The detailed observations that were made in the Rochdale works, on which one of the British Occupational Hygiene Society's (1983) figures was based, have been provided by Mr Reginald Sykes, a member of the committee that produced the society's report and senior manager (safety and environmental control) at the Rochdale works. We have used them to test the hypothesis that the ratio between the results obtained by personal and static sampling (and hence the conversion factor that relates measures of pollution obtained by the two methods) tends to diminish as the amount of pollution increases. We have, therefore, plotted the logarithm of the ratio against the logarithm of the geometric mean of each pair of observations and show the results in Fig. 4/4.* The correlation is

*Obtained by dividing the particle counts per ml by 35 to convert to mppcf. To bring the results into line with Sykes' formula which used particles ml^{-1}, we need to multiply the fibre count by 2.155, the figure given by Sykes to convert fibre counts obtained by the LRTP to counts obtained by modern membrane filter methods with graticule grid reading.

*To test the hypothesis that the difference between two measurements, x_1 and x_2, of the same quantity, both with normally distributed random error, is independent of q, the true value, it is usual to calculate the correlation between the arithmetic mean of the measurements $1/2(x_1 + x_2)$ and the difference $(x_1 - x_2)$. This avoids the spurious positive correlation between the initial reading x_1 and the observed change $x_1 - x_2$ that is produced by regression to the mean. Fibre counts, however, are distributed approximately log normally (Dagbert, 1976). If, therefore, we designate the logarithm of a personal count p and a parallel static measurement s by x_1 and x_2 respectively, a useful test of the independence of the personal to static ratio and the true dust level is provided by the correlation of the logarithm of their ratio, $x_1 - x_2$, against the logarithm of their geometric mean, $(x_1 + x_2)/2$.

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extremely poor (r = -0.051) due, however, to two outlying points that are based on exceptionally low and unreliable static sample readings. The four points with unreliably low readings (two static and two personal samples) are indicated separately in the Figure and if they are disregarded the correlation strongly suggests that the ratio diminishes as the mean increases and becomes less than one (ie the personal samples fall below the static) when the geometric mean of the readings approaches 2 f.ml^{-1}.

We have noted, too, that measurements at the Rochdale factory in 1971, when average dust levels in many areas exceeded 2 f.ml^{-1}, were reported as being consistently lower for personal than for static samples in most areas when yearly mean levels were compared. Smither and Lewinsohn's (1973) data are reproduced in Table 4/7 and, for the purpose of converting measurements taken at the static sampling points in this factory to those that would have been obtained by personal sampling in 1971 or earlier, these figures suggest that the past measurements would be more appropriately halved than doubled. It is unfortunately impossible to check these earlier data experimentally except by re-creating the working conditions and sampling procedures that obtained in the past, and this is hardly practicable. Parallel measurements in other factories, even if they were operating under poor hygiene conditions, would not be of much relevance.

The generalisation that personal measurements will usually exceed the results of static sampling by a factor of about two is, therefore, of doubtful relevance to the interpretation of static samples taken 20 or more years ago when average levels in most scheduled areas exceeded 2 f.ml^{-1}. Whether static measurements will, on average, be greater or less than those obtained by personal sampling will depend on whether the average of the dust levels at the various sampling points happens to be higher or lower than the average that the workers are exposed to as they move about the factory and will depend on the particular combination of work practices, sampling positions, and ventilation arrangements in the factory. In view of the many ambiguities, which are impossible to resolve, we have not felt justified in using any one conversion factor to allow for the changes in methodology and, for our present purpose, can relate the biological findings only to the measurements that were made at the time the relevant exposures occurred (Peto *et al*, 1985).

McDonald, who may be thought to have the most extensive experience of the problem of converting old particle counts to modern fibre counts, reported to the Royal Commission (1984) in Ontario that after "a good five or six years" during which he had attempted to obtain a satisfactory conversion factor, he was beginning to get depressed about the possibility of ever doing so, adding that "I think we know [now] how almost unanswerable the problem is." When so much work has been done in collecting and analysing measures of ambient pollution, we hesitate to suggest experience to the effects of current exposures. Nevertheless, this may, in fact, be the case and we may have to be satisfied with qualitative conclusions based on knowledge of the direction in which progress has been made and epidemiological observations of the effects of qualitatively different types of exposure.

Conversion of particle to fibre counts

In spite of the reservations discussed above, we are obliged to select a conversion factor from particles to regulated fibres for the purpose of dose-specific risk prediction. Leaving aside the dubious validity of any such attempt, the most appropriate procedure for estimating the conversion factor will depend on the use to which it will be put. Linear regression (perhaps weighted to allow for differences in variation at different levels) on the results of parallel measurements will give a reasonable prediction of the fibre count that would have been obtained under the conditions under which the data were collected, but random error in the original measurements will tend to flatten the slope below the true value and increase the constant in the equation. The formulae given in the previous section will therefore tend to give an overestimate of the fibre count at very low levels and an underestimate at high levels even if the underlying relationship is in fact linear, and it is preferable to constrain the fitted line to pass through the origin to avoid this bias. The simplest way to achieve this, and the one that we have adopted, is to use the ratio of the averages of the results obtained by the two methods. This is a robust procedure, particularly when random variation on both measurements is large, and the result is not dominated by one or two extreme values. Thus, for example, the correlation between the 1960 particle and 1961 regulated fibre counts is halved when the highest reading is omitted (see Fig. 4/3) but the ratio of the averages is hardly altered, falling from 34.0 to 33.0 particles/fibre. We chose to analyse the particle counts taken in 1960 and the regulated fibre counts taken in 1961 in the same areas rather than the parallel measurements taken in 1977, both because the 1960/61 data were collected routinely and because they included higher readings which were more representative of earlier conditions. Perhaps coincidentally, however, our preferred regression analyses of the 1977 parallel measurements gave a similar conversion factor (see p. 18). A value of 35.3 particles per fibre would mean that 1 mppcf is exactly equivalent to 1 f.ml^{-1} and we have, therefore, used this factor in our dose-response analyses to preserve this convenient identity.

Measures of response

What the epidemiological observations should be is, in principle, straightforward; but there is still need for research to discover the best way to record them for the purposes of international and temporal

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is to decide the criteria on which the diagnosis is made, and we leave consideration of that to Chapter 5; but for the latter, this is no longer of any major concern. Most cases of lung cancer and mesothelioma can be diagnosed with confidence (although the distinction between them is not always clear) and their clinical course is so rapid that it makes very little difference scientifically (and unfortunately very little difference to their fatal outcome) when they are first detected. Precise microscopic diagnosis is not always feasible, but other methods are reasonably reliable and the risk of overlooking either disease, which used to be substantial (as was noted in Chapter 3) is now quite small.*

The problem with cancer is not so much to know when it is present, as whether we should be measuring the absolute or the relative excess and how each measure varies with the time since exposure began and ended, the duration of exposure, and the age at which exposure first occurred. Neither evidence from the study of experimental carcinogenesis in animals nor theoretical considerations provide much help in answering these questions; partly because few experiments have been undertaken on a large enough scale to provide the answers, and partly because most experiments have tried to examine the effect of exposure under controlled conditions to one agent at a time, whereas people are exposed occupationally under conditions in which they are also exposed to a wide range of agents that may produce cancer in many other ways. [illegible]

exposure to an ambient concentration of (say) one fibre ml^{-1} for 25 years consequently requires a series of assumptions about the relative effect of varying the intensity and duration of exposure, the age at which exposure starts and stops, and the extent to which the effect of the fibres acts synergistically with, or independently of, other carcinogenic agents; and few of these assumptions can, as yet, be made on sound scientific grounds.

Note to Tables 4/1–4/3

The ratio of the number of deaths observed from lung cancer to the number expected in each study is shown in parentheses after the number of lung cancer deaths in excess (ie the difference between the numbers observed and expected). The expected numbers were mostly obtained by applying the corresponding sex and age (and if appropriate race) specific national mortality rates for appropriate calendar periods to the numbers of person years observed in the individual cohorts over the same periods. Exceptions which used local or regional rates, or adjusted the national rates by a local factor were: Acheson *et al*, 1982 (adjusted for locality); Finkelstein, 1983 (Ontario rates); Hobbs *et al*, 1980 (W Australian rates); Kolonel *et al*, 1980 (Hawaiian rates); McDonald *et al*, 1980 (Quebec rates), 1983a (S Carolina rates), 1983b (Pennsylvania rates), 1984 (Connecticut rates); McDonald and McDonald, 1982 (Ontario rates); Mancuso and Coulter, 1963 (Ohio rates); Peto *et al*, 1985 (adjusted for locality); Rossiter and Coles, 1980 (S West region of England rates).

* Some peritoneal mesotheliomas may continue to be overlooked, but pleural mesotheliomas are now so firmly identified with exposure to asbestos that, once such a history has been obtained, they may be more likely to be diagnosed inappropriately than missed (Wright *et al*, 1984; Peto *et al*, 1985).

le 4/1 Cohort studies of men and women exposed to chrysotile asbestos with little or no exposure to other types

...sure	Sex	Type of industry	No. of deaths observed	No. of lung cancer deaths in excess	No. of mesotheliomas: pleural	peritoneal	type unknown	Reference
	M	Mining and milling	3291[a]	46.0 (1.22)	10[b]	0	—	McDonald *et al*, 1980
	M	"	220[c]	0.3 (1.03)	1[f]	0	—	Rubino *et al*, 1979
other		Manufacture:						
posure	M	cement[d]	268	−0.8 (0.97)	0	0	—	Thomas *et al*, 1982
	M	paper & millboard	66	−0.3 (0.93)	0	0	—	Weiss, 1977
	F	gasmasks	177	1.2 (1.25)	1[g]	0	—	Acheson *et al*, 1982
	a)	Manufacture:						
	M	textiles	570[e]	29.4 (2.00)	0	1	—	McDonald *et al*, 1983a
	M	friction materials	803[e]	23.9 (1.49)	0	0	—	McDonald *et al*, 1984
	b) M	textiles[h]	850[e]	42.9 (1.61)	17	0	—	Peto *et al*, 1985
tile	M	textiles[h] &	912	12.9 (1.36)	8[i]	5	—	[i]Robinson *et al*, 1979
ther		friction materials						
xposure	M	"	1339[h]	3.5 (1.03)	8	0	—	Berry and Newhouse, 1983
	b) F	textiles[h]	49[h]	2.1 (2.11)	0	0	—	Peto *et al*, 1985
	F	textiles[h] and friction materials	128	12.3 (8.24)	1	1	2	Robinson *et al*, 1979
	F	friction materials	299[h]	−5.3 (0.53)	2	0	—	Berry and Newhouse, 1983

[a] Men first employed only after 1936 when use of crocidolite ceased.
[b] Chrysotile used from 1879, plus approximately 2.6% of crocidolite from 1932 to 1968.
[c] Chrysotile used from early 1900s, always 99% or more except during 3 years of war, when amosite increased from less than 1 to 5%; crocidolite always less than 1%.
[d] 20 or more years after first employment.
[e] 10 or more years after first employment.
[f] Subsequently increased to 14 pleural and 0 peritoneal over a longer period of observation (McDo... , 1979).
[g] Suspected only, excluded from lung cancer deaths.
[h] In a woman thought to have transferred to another factory where crocidolite was used.
[i] The same factory was studied by McDonald *et al*, (1983b) who included a larger cohort and followed them for longer. Robinson *et al* data are, however, preferred as McDonald *et al*, did not separate the mesothelioma cases from other causes of death. Their data suggest that the 4 mesotheliomas described by Robinson *et al* as of unknown site are likely to have been pleural.

Table 4/2 Cohort studies of people exposed mainly or entirely to crocidolite or amosite asbestos

Exposure	Sex	Type of industry	No. of deaths observed	No. of lung cancer deaths in excess	No. of mesotheliomas			Reference
					pleural	peritoneal	type unknown	
Only or mainly crocidolite	M	Mining	526	21.8 (1.57)	17[3]	0	—	Hobbs *et al*, 1980
		Manufacture: gasmasks	43	4.0 (2.00)[4]	—	—	8	McDonald & McDonald, 1981
	F	Manufacture: gasmasks[1]	156	6.4 (2.14)	13	4	—	Jones *et al*, 1980
		gasmasks	219	6.8 (2.10)	3	2	—	Acheson *et al*, 1982
		gasmasks	13	0.0 (—)	—	—	2	McDonald & McDonald, 1981
amosite	M	Manufacture: insulation	524	70.6 (6.29)	5	6	—	[5]Selikoff & Hammond, 1975
	M	insulation[2]	333	27.9 (1.96)	4	1	—	Acheson *et al*, 1984

[1] A small proportion of the women worked with chrysotile only (11%) or with both types (10%) and 11% has been deducted from the expected number of cases of lung cancer. None of the women who worked only with chrysotile developed lung cancer or mesothelioma. Tracing of the population was incomplete (578 traced out of 951) and subsequent personal communication to Acheson and Gardner (1983) reported 39 mesotheliomas (34 pleural, 5 peritoneal).

[2] The factory also used a small amount of chrysotile in 1946–73 (less than 3% of the total) and large amounts of lime, silica, and cement (totalling 60–80% of the product).

[3] In a later review of mesothelioma in Western Australia over the period 1960–82, Armstrong *et al* (1984) identified 56 mesotheliomas in men with exposure to the crocidolite mines or mills of which 3 were peritoneal; the corresponding excess of lung cancers is not yet known.

[4] Preferred to subsequent report by Seidman *et al*, (1979) because it identified the death certificate diagnoses of subjects with mesotheliomas. The later report gave 528 deaths with 7 pleural and 7 peritoneal mesotheliomas.

le 4/3 Cohort studies of people exposed to mixed chrysotile and amphibole asbestos or unknown types

osure	Sex	Type of industry	No. of deaths observed	No. of lung cancer deaths in excess	No. of mesotheliomas			Reference
					pleural	peritoneal	type unknown	
		Manufacture:						
	M	?product[1]	83	−4.2 (0.54)	2	0	—	Thomas *et al*, 1982
	M	textiles & insulation material	545[1]	59.8 (2.38)	19	27	—	Newhouse & Berry, 1979
rysotile	M	cement	58[4]	15.4 (6.92)	5[5]	5	—	Finkelstein, 1983
3	M	Insulation	83[2]	20.4 (3.75)	4	6	—	Newhouse & Berry, 1979
phibole	M	"	253[3]	36.0 (7.00)	3	4	—	Selikoff *et al*, 1964
	M	"	1946[3]	303.0 (4.24)	23[6]	24[6]	54[6]	Selikoff *et al*, 1979
	M	Shipyards	1043	−16.3 (0.84)	29	2	—	Rossiter & Coles, 1980
	M	"	112[3]	5.5 (1.73)	0	0	—	Kolonel *et al*, 1980
		Manufacture:						
	F	textiles	200[2]	23.8 (8.44)	13	8	—	Newhouse & Berry, 1979
		Manufacture:						
known	M	?product	166	9.6 (2.77)	0	6	—	Mancuso & Coulter, 1963
	F	"	20	3.8 (21.05)	0	1	—	Mancuso & Coulter, 1963

Limited to men first employed before 1936, when crocidolite was in use.
0 or more years after first employment.
0 or more years after first employment.
5 or more years after first employment.
Up to 3 of the mesotheliomas should be subtracted from the lung cancer excess.
The numbers of mesotheliomas are as given on death certificates. Further enquiry revealed an additional 69 cases 20 or more years after first exposure, at more than 8 of which should be subtracted from the excess lung cancers. The mesotheliomas of unspecified site on the death certificate were divided most equally between pleural and peritoneal sites, while the additional cases were almost all peritoneal (Selikoff, 1982).

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Table 4/4 Summary of results of cohort studies by type of fibre

Type of fibre to which exposed	Sex	No. of deaths observed	No. of lung cancer deaths in excess	No. of mesotheliomas: pleural	peritoneal	type
Only chrysotile	M	3845	45.2	11	0	—
	F	177	1.2	1	0	—
Nearly all chrysotile						
a) late introduction of amphibole	M	1373	53.3	0	1	—
b) early introduction of amphibole	M	3101	99.3	33	5	—
	F	476	9.1	3	1	2
Chrysotile and substantial amphibole	M	4123	419.6	85	68	54
	F	200	23.8	13	8	—
Only or mainly crocidolite	M	569	25.8	17	0	8[1]
	F	388	13.2	16	6	2[1]
Only amosite	M	857	98.5	9	7	—

[1] According to McDonald and McDonald (1978) 6 out of 9 mesotheliomas then diagnosed in these series were peritoneal and two-thirds have been classed as peritoneal for the purpose of the analysis in Table 4/5.

Table 4/5 Condensed summary of results of cohort studies by type of fibre

Type of fibre	Per cent of total deaths: excess lung cancers		mesotheliomas		Ratio of peritoneal to pleural mesotheliomas	
	M	F	M	F	M	F
Chrysotile alone	1.18 (1.89)[a]	0.66	0.29 (0.23)	0.56	0.00 (0.09)	0.00
Principally chrysotile	2.52 (1.91)	1.91	0.87 (1.23)	1.26	0.20 (0.17)	0.33
Chrysotile and substantial amphibole	10.11	11.90	5.02	10.50	0.80	0.62
Solely or principally amphibole	8.72	3.40	2.88	6.19	0.43	0.44

[a] Figures in parentheses show the proportions that would be obtained if industries with late introduction of amphiboles were classed with those using chrysotile only.

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Table 4/6 Amount of asbestos fibre in lungs of men dying of mesothelioma or of conditions unrelated to asbestos exposure in North America in 1977* (after McDonald, McDonald, and Pooley, 1982)

Amount of fibre (fibres/g)	Chrysotile fibres		Amosite fibres		Crocidolite fibres		Chrysotile fibres in lungs with less than 1 fibre/g amphibole fibres	
	No. of subjects		No. of subjects		No. of subjects		No. of subjects	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
< 1	11	12	50	68	61	71	7	8
1–	38	38	14	7	6	5	26	24
10–	25	22	8	1	8	0	14	12
100–	2	2	3	0	1	0	0	3
1000 or more	0	2	1	0	0	0	0	0
Any	76	76	76	76	76	76	47	47

* Unlike in Britain, amosite has been used more widely than crocidolite.

Table 4/7 Dust levels—Rochdale asbestos textile factory—1961, 1966, 1971 (Smither and Lewinsohn, 1973)

Department	Process	Yearly mean dust levels (fibres/ml)			
		Long-running thermal precipitator and membrane filter		Static sampler	Personal sampler
		1961	1966	1971	1971
Fibrising	Bag slitting	4.5	4	3	1
	Mechanical bagging	4.0	4.5	4	1
Carding	Fine cards	5.5	5.5	3.5	2
	Medium cards	7.5	8	4.5	3.5
	Coarse cards	7.0	7.5	8	6
	Electrical sliver cards	5.0	2	1.5	1
Spinning	Fine spinning	4	3.5	2.5	3
	Roving frames	5.5	5.5	6	3
	Intermediate frames	5.5	5.5	5.5	3
Weaving	Beaming	8	3.5	0.5	0.5
	Pirn weaving	3	2.9	1.5	1
	Cloth weaving	3	2	2	1
	Listing weaving	2	1	0.5	0.5
Plaiting	Medium plaiting	4	4	4	2

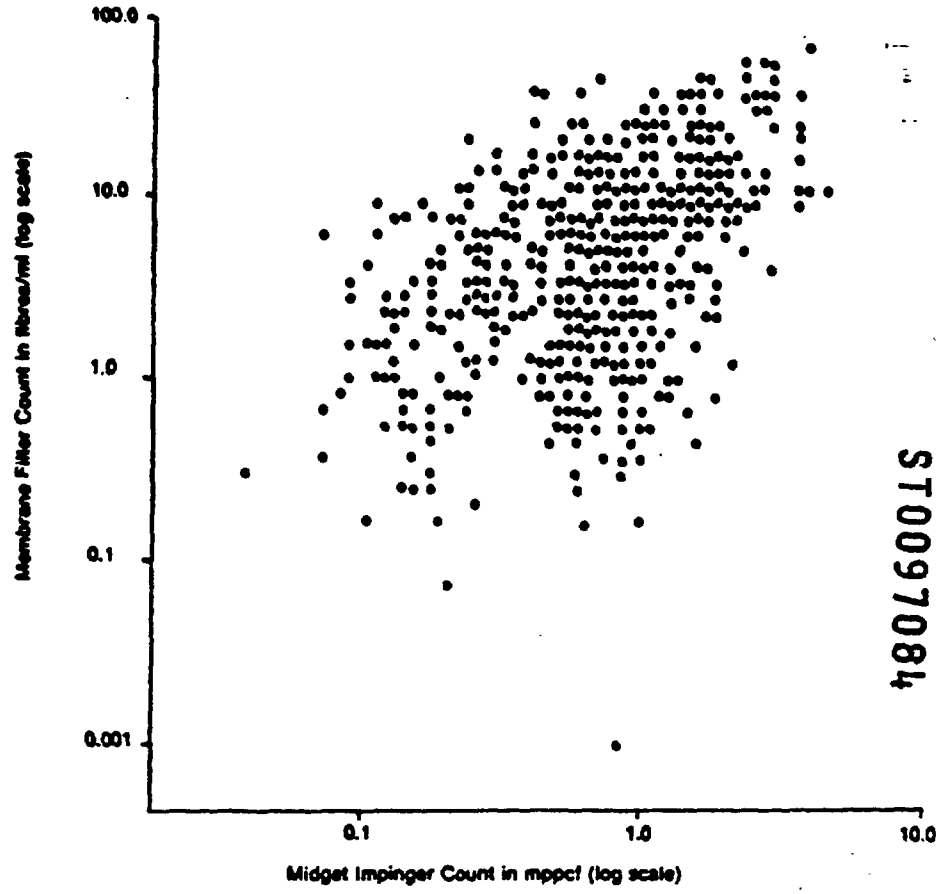

Fig. 4/1 Relationship between amount of pollution in seven Quebec mines obtained from 623 parallel measurements by the midget impinger, as million particles per cubic foot, and a membrane filter, as regulated fibres per ml: log-log scale. (Reproduced from Dagbert, 1976, with the permission of the author.)

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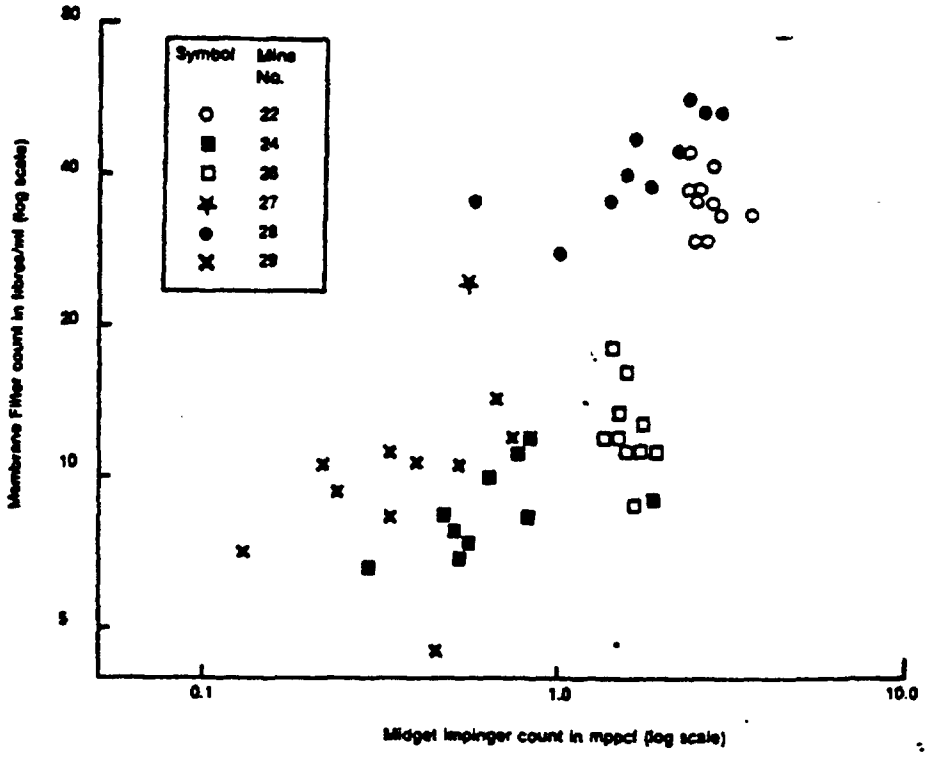


Fig. 4/2 Relationship between amount of pollution in six Quebec mines obtained for the process of "fibre screening", by parallel measurements with the midget impinger, as million particles per cubic foot, and a membrane filter, as regulated fibres per ml: log-log scale. (Reproduced from Dagbert, 1976, with the permission of the author.)

Fig. 4/3 Relationship between amount of atmospheric pollution in 18 different parts of the Rochdale asbestos textile factory measured in million particles per cubic foot by the Casella thermal precipitator in 1960 and in fibres per ml measured by the Ottway long running thermal precipitator in 1961.

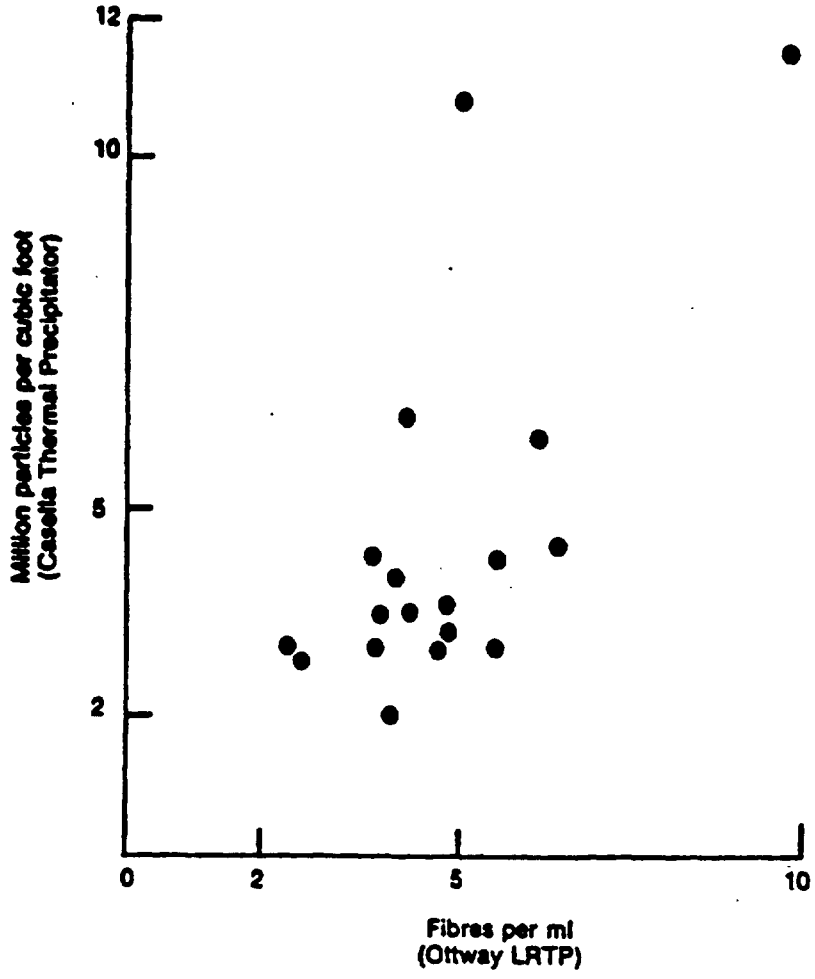
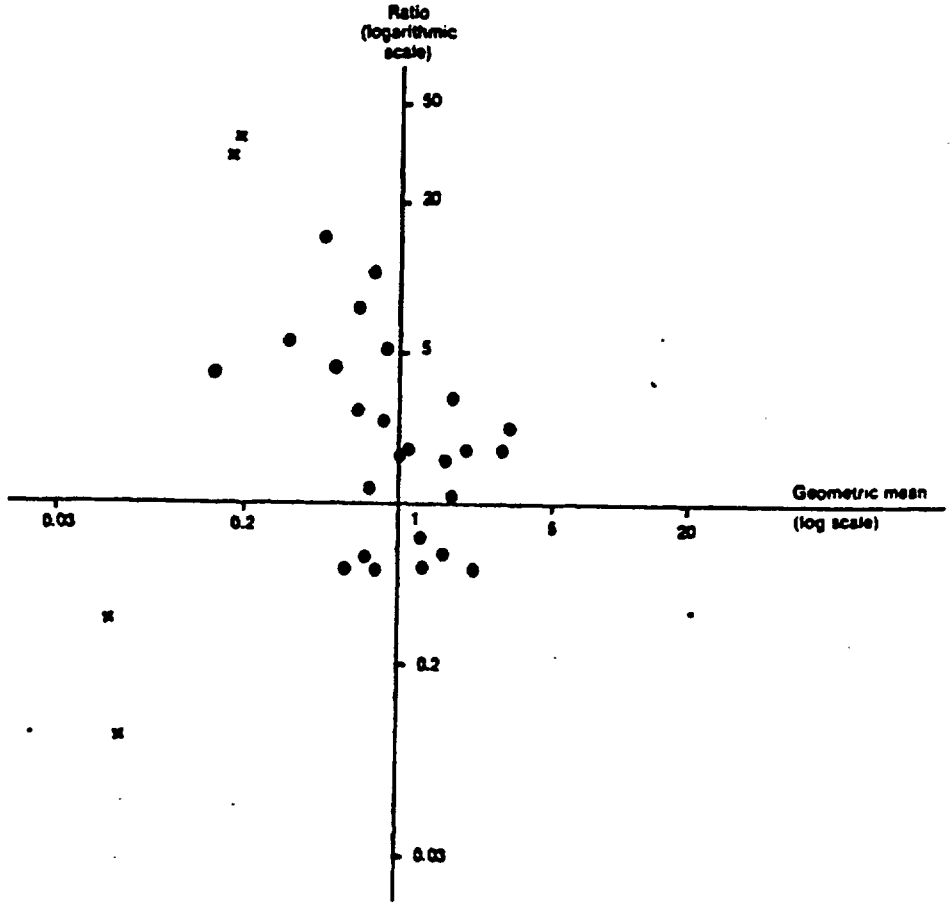


Fig. 4/4 Relationship between measurements of ambient pollution by asbestos fibres obtained simultaneously from static samples and nearest operative's personal sample in a Rochdale asbestos textile factory in 1977: logarithm of ratio of measurements (personal to static) plotted against logarithm of geometric mean of each pair of counts. Unreliable observations based on very low values for either static or personal samples shown as x.



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Asbestosis

The description of a dose-response relationship requires, by definition, measurement of both the doses to which groups of individuals are exposed and the frequency of occurrence of the corresponding responses. In the case of asbestosis, the description is made peculiarly difficult, as it is not only difficult to assess the dose to which individuals have been exposed in the past, but there is also a lack of any sharp dividing line between people with and without the disease, as was noted in Chapter 2.

The precautions that have already been taken have virtually eliminated the gross disease that led to early death in the past, and it is encouraging to note that no deaths from asbestosis have been observed in the men and women who have been studied in an asbestos textile factory in Rochdale, who were first employed after 1950 (Table 5/1 and note to Table) (Peto *et al*, 1985). This is, indeed, a sharp contrast with the 13% of men who died from the disease when they had been employed for more than 20 years in scheduled areas, with at least 10 years' employment before 1933. The early figures for asbestosis were, moreover, almost certainly underestimated, as the mortality from circulatory disease, which could hide unrecognised deaths from asbestosis masquerading as right heart failure, was nearly twice normal in this subgroup while in subsequent groups it was close to the expected value for the town (about 18% above the national average; Peto *et al*, 1985). The lack of deaths attributed to asbestosis in the post-1950 population cannot, however, be taken to imply that fatal cases will no longer occur. This may be so, but the development of the disease is commonly slow, and only two deaths from asbestosis would yet have been expected to occur in the post-1950 population, if the rate had remained at the same level as in those who were first employed between 1933 and 1950.

Asbestosis is not, of course, necessarily a fatal disease, and it would be possible for it to cause disability, or to increase the death rate from other respiratory and circulatory disease, without any deaths being specifically attributed to it. In this respect it is notable that asbestos acts synergistically with cigarette smoking to produce non-malignant non-infectious pulmonary disease, although the synergism is not as strong as it is for lung cancer. The death rate from asbestosis and the prevalence of signs and symptoms attributable to it are both higher in cigarette smokers than in non-smokers (Hammond *et al*, 1979; Berry *et al*, 1979) which adds to the already complex problem of measuring the incidence of the disease in its early stages.

The best evidence relating non-fatal asbestosis to different levels of exposure is that previously reported by Berry (1977) and published by Acheson and Gardner (1979) in the advisory committee's report and subsequently published by Berry *et al* (1979) in greater detail. This led the committee to conclude that "an annual incidence of 0.5% (standard error (SE) 0.2%) certified asbestosis has occurred after cumulative doses of less than 100 fibre years per ml, ie within a working life at 2 fibres per ml. The annual rates of incidence for 'possible asbestosis' and 'crepitations' are higher at any given level and suggest the possible occurrence of asbestos-related disease at cumulative doses of less than 50 fibre years per ml". No evidence has been obtained since then to alter this conclusion materially.

The British Occupational Hygiene Society's (1983) study, which consisted largely of observations on the same men that had been studied by Berry *et al* (1979) adds nothing that either strengthens or detracts from the committee's conclusion. What it does do, is to provide useful data on the relationship between fibre concentrations measured by static and personal samplers, demonstrate the amount of interobserver error in reading chest x-rays for signs of asbestosis, and show which of a number of radiological, lung function, and clinical changes are of value in distinguishing individuals who have been exposed to asbestos.

The only point on which we might disagree with Acheson and Gardner is the tentative conclusion in their 1979 report that there is no threshold dose for chrysotile "within the range experienced in industry" for the production of signs and symptoms of asbestosis. Berry *et al* (1979) used three sets of criteria for the diagnosis of asbestosis in increasing order of severity: (a) basal crepitations alone; (b) a combination of findings labelled "possible asbestosis" on the basis of the reports of the factory doctor reviewed by an independent expert which (although insufficient to satisfy the Pneumoconiosis Medical Panel) generally leads to a recommendation for the worker concerned to be transferred to a less dusty job; and (c) a certification by the Pneumoconiosis Medical Panel of disablement due to asbestosis. This last requires an adequate history of exposure, evidence of disablement, and two of the following: basal rales (crepitations), finger clubbing, certain specified radiological appearances, and alterations in lung function. All these changes can be produced by other conditions, and the recognition of them, other than the history of exposure and the alterations in lung function, is, to a certain extent, subjective and subject to inter and intraobserver error (see, for example, Smyllie *et al* (1965) and Loudon and Murphy (1984) on rales, Pyke (1954) on finger clubbing, British Occupational Hygiene Society (1983) on radiological appearances). It is conceivable, therefore, that the recognition of these signs is influenced by knowledge of the history of exposure. It follows that before we can be confident that low levels of cumulative exposure of the order of 50 f.ml^{-1} years or less do, in fact, produce recognisable

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disease we need a complex study, comparable to the one undertaken by Berry *et al* (1979), but including an unexposed population and with provisions for those in whom specified changes are thought to have taken place, and a sample of those in whom they are thought not to, to be referred for examination to independent specialists who are kept in ignorance of the employment history. Such a study may prove impractical, but, without it, it will be very difficult to be sure that biological effects of any material importance are produced by exposure to 1 f.ml^{-1} per year or less.

The fact that there have been no clinical cases of asbestosis among the general public led the advisory committee to accept, in 1979, that there may be a threshold level below which asbestosis is not detectable, and this conclusion is reinforced by the failure to detect any cases in over 600 members of the families of asbestos workers in the US (Anderson *et al* (1979)). The Royal Commission (1984) on Matters of Health and Safety Arising from the Use of Asbestos in Ontario, concluded that "At low levels of occupational exposure to asbestos the fibrotic process in the lungs, if indeed it can be initiated, will not likely progress to the point of clinical manifestation or even the mildest discomfort. On the basis of the available data, our best judgement as to the lifetime occupational exposure to asbestos at which the fibrotic process cannot advance to the point of clinical manifestation of asbestosis is in the range of 25 f/cc-yrs and below."

The data for signs and symptoms of early asbestosis do not suggest a threshold, but are ambiguous because they can all occur (and frequently do) in the absence of asbestos exposure. On common sense, rather than epidemiological, grounds we conclude that there may well be a threshold below which the ratio of significant asbestosis to asbestos-induced cancer becomes either zero or so low that asbestosis should be ignored when estimating the long term effects of exposure. The evidence suggests that this is likely to be true for the fibre counts that are likely to occur in the future and we, therefore, see no reason to disagree with the conclusion of the Ontario Royal Commission.

Cancer

In estimating a dose-response relationship for lung cancer and mesothelioma we are faced with a set of problems that are, in many respects, different from those presented by asbestosis. There is little difficulty in knowing when either disease has occurred, but (as was discussed in Chapter 4) great difficulty in deciding how to take account of age at exposure, duration of exposure, and time since exposure began, what allowance to make for different fibre sizes and types, and (in the case of lung cancer) how to take account of the effects of cigarette smoking. In spite of these difficulties some formal model has to be adopted for each disease if we are to provide estimates of lifelong risk and to extrapolate from observations, such as those obtained in our study, to predict the effects of brief exposure or prolonged exposure at low levels.

The problem would be simplified if intensity and duration of exposure could be combined in a single index such as cumulative exposure; but the use of such an index implies several rather strong assumptions and would, for certain carcinogens, lead to gross error. Thus, for example, the increase in lung cancer risk caused by smoking 10 cigarettes a day for 50 years may be two orders of magnitude greater than that caused by smoking 50 cigarettes a day for 10 years.

For both lung cancer and mesothelioma, there is clear qualitative evidence that excess mortality is increased by more intense exposure, but available data are not sufficiently detailed to establish the form of dose-dependence. We shall assume for both diseases that the increase in risk is directly proportional to intensity (dust level) for an exposure of fixed duration at a given age. This is consistent with available data, including our own (Peto *et al*, 1985), but there are examples of both upward and downward curvature in dose-response for other carcinogens, and the assumption of dose-linearity, although scientifically plausible, is not demonstrably correct. Nor is it demonstrable that there is no threshold dose below which cancer is not produced. The idea that there might be such a dose and that asbestos induced cancers occur only secondary to the fibrosis of asbestosis has sometimes been expressed. The idea originated in the days before the discovery of DNA, when cancers were not thought to result from genetic variation in somatic cells, but from the repair of tissue damage that was macroscopically visible. In the light of modern knowledge of carcinogenesis such an idea does not seem plausible. No threshold for the carcinogenic effect of asbestos has been demonstrated in humans or in laboratory animals and, in the absence of positive evidence for a threshold, we have followed standard scientific practice and assumed that none exists. One possible reason for thinking that asbestos induced cancers might be secondary to asbestosis is the high incidence of cancer in the similar condition of cryptogenic fibrosing alveolitis. As, however, the aetiology of this disease is unknown, the argument by analogy does not carry much weight and we have ignored it.*

Differences between fibre types and industries

The evidence on differences between different fibre types and industrial processes is reviewed in Chapter 4. The principal conclusions are:

(a) peritoneal mesothelioma is rarely or never caused by chrysotile exposure;

(b) crocidolite and amosite are more dangerous than chrysotile when used in the same way;

* If cryptogenic fibrosing alveolitis proves to be caused by the Epstein-Barr virus as Vergnon *et al* (1984) suggest, the analogy would collapse.

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(c) there are marked differences between different studies in the ratio of the number of pleural mesotheliomas to the excess of lung cancer. The highest reported ratio based on substantial numbers of cases occurred in English dockyard workers who were exposed to a mixture of types of asbestos (Rossiter and Coles, 1980) and the lowest in American textile workers who were exposed to very little other than chrysotile (McDonald *et al*, 1983a); but this cannot be attributed entirely to differences between chrysotile and other types of asbestos as the effects of chrysotile alone also appear to vary. In the American textile workers, just referred to, the ratio was zero (0/29.4), while in Canadian chrysotile miners (McDonald *et al*, 1980) it was 0.22 (10/46.0). Fibres of different dimensions are likely to reach, and perhaps also to migrate from, the upper bronchus and the pleura differentially, and such differences might therefore be expected. The site-specific effects of fibres of different sizes and types have, however, not yet been determined; and

(d) the marked difference in lung cancer risk between workers handling textiles (McDonald *et al*, 1983a) and friction products (McDonald *et al*, 1984; Berry and Newhouse, 1983) at similar nominal exposure levels and all exposed almost entirely to chrysotile are unexplained. They could be due (at least in part) to differences in the proportion of pathogenic fibres that are counted with the normal optical microscope, or to other differences in the proportion of fibres of different configurations.

These conclusions suggest that the effect of fibre size should be included in our models, and that the effects will not be the same for lung cancer as for mesothelioma. In common with previous authors, however, we do not have any useful data on the distribution of fibre sizes 30 or more years ago in the facory that we have studied, and can therefore only draw attention to this major defect in any extrapolation of dose-specific risks from one industry to another or from occupational to environmental exposure.

Mesothelioma

Factors influencing incidence

Time since first exposure and age

Observation of the incidence of mesothelioma in North American insulation workers suggest that the incidence of the disease increases approximately in proportion to a power of the time elapsed since exposure first occurred irrespective of whether the duration of exposure was short or long, and that the best fitting power for the large number of patients studied was 3.2 (SE 0.4) (Peto *et al*, 1982). This can be explained on the assumption that each brief period of exposure causes an addition to subsequent incidence that increases approximately as the cube of time since the exposure occurred. Under this model, incidence would rise as the cube of time since first exposure following brief exposure and as the fourth power of time during continuous exposure; for exposure lasting five or 10 years the incidence would be well approximated by a power of time of between three and four (Peto, 1983).* Unlike cancer of the lung, the risk appears to be independent of smoking habits (Hammond *et al*, 1979) and it is also independent of the age at which exposure first occurs.

If incidence is linearly proportional to dose, this model predicts that the incidence I(t) at age t caused by exposure at a constant dust level L beginning at age t_1 and ending at age t_2 will be given by the equation

$$I(t) = kL[(t - t_1)^n - (t - t_2)^n]$$

where k is a constant (Peto, 1983). The predicted risk increases in approximate proportion to duration for exposures of up to about 10 years, but more slowly thereafter and there is very little difference between the predicted effects of stopping or continuing exposure after 20 years.

Duration of exposure

The effect of mesothelioma incidence of different durations of exposure has not been studied extensively and it is not clear whether this model provides an accurate prediction of the relative effects of different durations of exposure. Our own data, which are reproduced from Peto *et al* (1985) in Table 5/2, are consistent in showing little difference between exposure of 10 to 20 years' duration and longer intervals, but they suggest that the risk caused by brief exposure may be rather lower than would be predicted. Stopping exposure to a carcinogen which causes cancer to an equal extent irrespective of age at exposure, as is the case with asbestos and the induction of mesothelioma, sometimes produces a marked and abrupt reduction in the subsequent rate of increase of incidence, probably because such agents sometimes affect a late as well as an early stage in carcinogenesis. Thus, for example, lung cancer incidence remains roughly constant after stopping smoking. It is, however, difficult to predict the effects of stopping exposure to asbestos, as amphibole asbestos remains in the body for many years; but if a late stage in mesothelioma induction were dependent on the residual tissue burden, a disproportionately low risk following brief exposure to chrysotile might be

*The exponent of time may not have been estimated accurately, but for practical purposes this is not important. The incidence is estimated most precisely 30 or more years after first exposure and the subsequent incidence rates predicted by exponents of between three and five do not lead to very different estimates of life-long risk. For a given incidence 35 years after first exposure, the predicted risk of developing mesothelioma by age 80 years, for a man aged 20 years at first exposure, would be reduced by 21% if the exponent of time since first exposure was reduced from four to three and increased by 36% if the exponent was increased to five. In older recruits the variation would be less.

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expected, as the tissue burden of chrysotile is substantially reduced once exposure has stopped. The model we have used for mesothelioma is only one of several scientifically plausible alternatives, but it has the advantage that it accounts for the observed pattern of incidence caused by prolonged exposure in an industrial context.

A progressive reduction in mesothelioma risk as duration of exposure is reduced has also been demonstrated in other studies (eg Newhouse and Berry, 1976; Hobbs *et al*, 1980), and this observation deserves special emphasis. For it is still widely believed, in spite of consistent evidence to the contrary, that very brief asbestos exposure necessarily causes a substantial risk of mesothelioma. Cases have occasionally been caused by short very intense exposure to amphiboles, but under most circumstances the risk caused by brief exposure is negligible.

Dose-specific risk

As far as we are aware, no attempt to analyse the dose-specific mesothelioma risk based on individual exposure estimates has been published, although several studies have shown a qualitative relationship between risk and intensity of exposure. Our data are consistent with a linear relationship (Peto *et al*, 1985), which is the model we have adopted for the purpose of extrapolation. If we assume a conversion factor for Rochdale of 35.3 thermal precipitator particles to one regulated fibre (or 1 mppcf to 1 f.ml^{-1}) our results lead to an estimate of k of 1.24×10^{-10} in the formula given previously on p. 5/11, when L (the level of ambient pollution) is measured in regulated fibres per ml.

The ratio of mesotheliomas to excess lung cancers 20 or more years after first exposure in the Rochdale cohort (17 to 28.43; see Table 4/1) was high compared with that in cohorts almost exclusively exposed to chrysotile. As we have indicated in Chapter 4, we believe that chrysotile can cause mesotheliomas. There is, however, consistent evidence that the risk of developing the disease is increased disproportionately in chrysotile workers who have also been exposed to small amounts of amphiboles, particularly of crocidolite. We, therefore, suspect that the high incidence in the Rochdale cohort is atypical of chrysotile workers and was due, in part, to the limited exposure to crocidolite that occurred in the factory. The data for other cohorts have not been published in sufficient detail to enable us to pool them with the Rochdale data and, for the practical purpose of calculating (in Chapter 6) the risks that men exposed to specific doses of pure chrysotile are likely to have, we have arbitrarily halved the mesothelioma incidence that we observed to allow for the exposure to crocidolite. Our predictions of the incidence of mesothelioma following exposure to a given amount of chrysotile are, therefore, derived from the formula

$$I(t) = 0.62 \times 10^{-10} L[(t - t_1)^4 - (t - t_2)^4]$$

... pollution and t...

This seems a sensible compromise between the extremes of using only our own data, which are incompatible with McDonald *et al*'s (1983a), and of attributing all mesotheliomas in chrysotile workers to possible exposure to amphiboles. This view is further supported by our observations on men who had worked at Rochdale for 10 or more years before 1933, which confirm that chrysotile alone can cause mesothelioma, but that the ratio of mesothelioma to excess lung cancer (two mesotheliomas against an excess of 11.42 lung cancers; Peto *et al*, 1985) is lower when exposure is almost exclusively to chrysotile. These men, who were originally studied by Doll (1955), were very heavily exposed to chrysotile before 1930, when some crocidolite was first used in the factory. The first of these two mesotheliomas occurred in 1936, and this case, at least, seems likely to have been caused by chrysotile. Our specific assumption that 50% of the mesotheliomas in men employed in 1933 or later were due to crocidolite is, however, certainly questionable and emphasises yet again the uncertainty of any current dose-specific estimates of risk.

Lung cancer

Factors influencing incidence

The assumption that asbestos increases the relative risk for lung cancer in proportion to both duration and average intensity of asbestos exposure, irrespective of both age and cigarette smoking (Peto, 1977 and 1978) has been adopted in several recent reviews (Acheson and Gardner, 1979 and 1983; Chronic Hazard Advisory Committee on Asbestos, 1984; Royal Commission, 1984; National Research Council, 1984). This model embodies several quite strong assumptions:

(a) the relative risk for lung cancer increases linearly during exposure at a constant level and remains constant after exposure has ceased. Brief intense exposure therefore causes an abrupt and persistent increase in relative risk;

(b) the relative risk is independent of both age at exposure and smoking. (The absolute risk will therefore be strongly dependent on both, as it is in individuals not exposed to asbestos.);

(c) the increase in relative risk caused by a given intensity of exposure (dust level) is proportional to duration of exposure; and

(d) the increase in relative risk caused by a given duration of exposure is proportional to (average) intensity of exposure.

These assumptions are discussed in the following sections.

Time since first exposure

Little if any excess risk is produced for at least five years after first exposure, even under conditions of ... heavy exposure, and the increase in risk caused

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detectable for 15 or 20 years. This is apparent in our own data, which are reproduced from Peto *et al* (1985) in Table 5/3. The delay is of little importance in calculating lifelong risks, as the expected probability of dying of lung cancer during the five years following first exposure is usually low; but it suggests that exposure during the five years before death should be ignored in analysing dose-response, and we have adopted this convention in our analyses.

Duration of exposure

The greatest risks are usually observed after more than 10 years' exposure and, for the purpose of calculating lifelong risks, we shall adopt the generally accepted convention that the relative risk rises progressively with continuous exposure, over a period of at least 30 years. There is, however, some evidence to suggest that this is not necessarily always true. If the assumption is wrong, this may be expected to reduce the risk that is actually experienced by long-term workers for a given cumulative exposure below that estimated, thus providing a further safety factor for any control limit, although the risk to short-term workers might then be underestimated.

The risk among short-term workers, for whom some anomalous observations have been recorded, is of special concern for two reasons. First, and most important, many workers who are exposed to asbestos at some time in their working lives are exposed for less than five years, so that if they suffer a disproportionately high risk their total contribution to occupationally induced mortality may exceed that contributed by long-term employees. Second, the detection and assessment of occupational risk is often based on the comparison of the mortality rates experienced by short- and long-service workers and if, for any reason, the risk in short-term workers is disproportionately high this will tend to reduce the correlation between risk and duration of employment and diminish the relationship with total dose. In fact, a disproportionately high lung cancer risk following short term exposure has been observed in several cohorts of asbestos workers, including our own (Table 5/3) and those reported by Seidman *et al* (1979) and by Acheson *et al* (1984) and also in men exposed to occupational hazards from beryllium (see Saracci, 1984) and zinc chromate (Davies *et al*, 1984).

An excess relative risk in short-term workers, which at Rochdale occurred only in men first employed before 1951, could be due either to a real increase in occupational risk, or to the use of inappropriate rates in the calculation of expected numbers, or to both. If the increase is real the assumption of proportionality between cumulative dose and excess risk should perhaps be modified; but even a real effect could be an artefactual distortion of a linear dose-response relationship if short-term workers were given the dirtiest jobs and were particularly careless in their handling of asbestos.

The alternative explanation is that short-term workers suffer the converse of the "healthy worker" effect due to atypical smoking habits, previous occupational exposures, or other "lifestyle" differences compared with the general population. Such differences could account for quite large differences in relative risk for certain diseases, but for lung cancer it is unlikely that a relative risk exceeding about 1.5 could be explained in this way, at least in Britain in recent years, where lung cancer rates are now among the highest in the world.

We interpret the small increase in relative risk in men exposed for less than a year in the cohort we have studied to a combination of chance and selection bias (Peto *et al*, 1985); but the much higher risk observed in workers exposed for between one and five years at higher dust levels reported by Acheson *et al* (1984) (SMR = 3.58, based on eight cases; $P<0.01$) and the doubled risk in men employed for only a few months reported by Seidman *et al* (1979) cannot be explained in this way. One possible explanation might be that at very high dust levels the lungs become saturated, the relative risk quickly reaches a high level, and further exposure has relatively little additional effect, whereas at lower exposure levels the relative risk continues to rise during continuing exposure. Such saturation with asbestos fibres that persist in the lungs for long periods, as amphiboles certainly do (and both the cohorts reported by Seidman *et al*, 1979, and Acheson *et al*, 1984, were amosite workers) could thus explain both a lack of much increase in risk with continuing exposure and an abrupt increase in relative risk, both of which seem to be characteristic of very heavily exposed workers. We are reluctant to suggest that "latency" is dose-related in this way, as almost all other observations on both human and animal carcinogens suggest that the time-dependence of cancer incidence is independent of dose-rate; but whatever the explanation of these effects, it appears that data on very heavily exposed workers may not provide a useful basis for predicting the risk at lower exposure levels.

A detailed review of these issues deserves serious attention; but it is beyond the scope of this report. Meanwhile, we believe that it is more appropriate, at least under conditions of low or moderate exposure, to compare the excess risk in long service workers against that of men exposed for about one to five years, or against local population rates, rather than to use men who worked for less than a year as low exposure "controls"; but whether this is right or not remains an open question.

Cessation of exposure

The assumption that the relative risk will remain constant after exposure has ceased is open to serious doubt. Our data show a substantial reduction in relative risk beyond about 35 years after first exposure and an eventual fall in relative risk has also been observed in other studies (see Walker, 1984 for review). This phenomenon cannot easily be attributed to the elimination of heavy cigarette smokers and of the most heavily exposed men, at least not in our data, and these observations raise the possibility that

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elimination or inactivation progressively reduces the carcinogenic effect. The excess relative risk may thus be more closely related to residual lung burden than to inhaled dose. In this case the reduction in relative risk might be expected to be most marked for chrysotile, which disappears from the lung after exposure has ceased more quickly than amphiboles. Few cohorts are, however, large enough for the effects of time since stopping exposure to be examined in detail and there are other possible explanations for the eventual fall in relative risk.

Cigarette smoking

Data on the combined effects of smoking and asbestos exposure have recently been reviewed by Berry *et al* (1984). We concur with these authors' conclusion that the observed increase in relative risk (allowing for smoking) caused by asbestos exposure has usually been rather greater in non-smokers than in smokers, and that this difference may be partially, and perhaps entirely, due to methodological artefacts, the most important of which is probably the misclassification of some current or ex-smokers as lifelong non-smokers. We are inclined to believe that the effect is in fact close to being exactly multiplicative (ie that the relative risk is the same for smokers as for non-smokers) as is suggested by the largest study in which smoking habits were obtained prospectively (Hammond *et al*, 1979). Whether this is exactly true is, for practical purposes, unimportant, as the risk to non-smokers is relatively small even after quite heavy asbestos exposure. Thus, for example, among North American insulation workers lung cancer contributed 30% (209/708) of all deaths among smokers and only 5% (5/94) of all deaths among lifelong non-smokers (Hammond *et al*, 1979).

Age

The eventual relative risk for lung cancer is certainly not strongly related to age at first exposure to asbestos. Among North American insulation workers, for example, the overall relative risk was 6.5 among men first exposed below age 25 years and 4.9 among those first exposed at older ages (Peto *et al*, 1982) a small difference which could be entirely due to differences in duration of exposure. Our own data (Peto *et al*, 1985) also show no effect of age at first exposure. (The relative risk beyond 20 years after first exposure for men exposed for 10 or more years in scheduled areas whose ages at entry were under 25, 25–34 and 35 years or over were 2.1, 2.0, and 2.1 respectively).

The primary aim of our report is to make some prediction of the likely consequences of prolonged industrial exposure and, as the eventual effect of exposure at older ages is similar to or less than that of exposure beginning at about age 20 years, we shall assume that age is irrelevant in our calculations of lifelong risk. The issue is of scientific interest, however, workers suggest that the relative risk beyond five or 10 years after first exposure eventually declines with increasing age, but is otherwise independent of time since first exposure (Table 5/4), and such an age-specific model for relative risk, adjusted for duration of exposure, might explain both the initial rise and the eventual reduction in relative risk observed in other cohorts.*

Dose-response relationships in medical literature

The major difficulty in assessing the validity of most other dose-response studies is the lack of any detailed account of the sampling procedures for measuring the ambient pollution and the results obtained. The only studies for which the results of extensive early sampling have been published and comparisons made of particle and fibre counts are those on chrysotile miners and millers in Quebec and chrysotile textile workers in South Carolina. These data, together with those for Rochdale (Peto *et al*, 1985), are therefore discussed below.

Rochdale textile workers

The difficulties involved in obtaining a quantitative measure of an individual's exposure to asbestos are not always appreciated and we, therefore, include here some details of the way our estimates were made, taken from the report of our study (Peto *et al*, 1985).

The exposure data available to us are in many respects similar in quality to those relating to chrysotile miners and millers in Quebec (McDonald *et al*, 1980; Dagbert, 1976) and are probably superior to any available for other cohorts in which a substantial increase in risk has been observed. Routine sampling of particle counts using a thermal precipitator at 23 fixed sampling points began in 1951 and between 18 and 25 samples were taken annually at each sampling point in the years 1952–1955. The number of sampling points, sampling frequency, and method of measurement varied in later years (see Chapter 4). Detailed studies of the results of parallel methods of measurement were conducted in 1977, although, for the reasons discussed in Chapter 4, we suspect that the comparison of routine measurements obtained by different methods in successive years may provide a more reliable (although still far from satisfactory) conversion factor. Annual averages at selected sampling points between 1952 and 1972 suggest that the substantial variation sometimes observed between average levels measured with the same instrument in successive years is due more to real differences in average levels than to random error, as there is a marked correlation between the patterns of fluctuation observed at different sampling points within the same area. Such changes did not usually occur at the same time in different areas, however, and they seem unlikely to

* Age-specific differences in lung cancer incidence are likely to reflect the effect of duration of smoking and its interaction with asbestos

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have seriously biased the overall averages for 1960 and 1961 on which our particle to fibre conversion is based. A disturbing aspect of these data (which for the period after 1960 have been converted from fibres to particles using the conversion factor of 35 particles to one regulated fibre; that is 1 f.ml^{-1} = 35 p.ml^{-1} = 1.0 mppcf, obtained by averaging the 1960 and 1961 results—see Chapter 4) is the large difference observed in certain areas when the membrane filter results obtained in 1965 are compared with the results obtained in 1964 or 1966 by other nominally comparable methods (long running thermal precipitator or automatic counter—see Chapter 4). These differences may be real, but it seems more likely that they reflect the unreliability of uniform conversion between different methods of measurement.

Selected sampling points that provided similar results were grouped together, giving a classification into four categories for each five-year period since 1951. For each period, jobs were assigned to the category that was judged to be most representative by a senior staff member in the health physics department at the factory. For most jobs this was unambiguous, as in many areas the majority of sampling points gave results in the same range, and most occupations involving exposure exclusively or predominantly in such areas could be assigned with reasonable confidence. Jobs that involved substantial exposure at various levels, or in areas where sampling was not conducted, were assigned on the basis of personal judgement. The primary basis for classification was the "prefix number", a three or four digit employment code that specified the area and type of employment. When this was not recorded, the block (ie section of the factory) and department coding was used. Jobs for which the block and/or department were not specified were classified individually.

This procedure suffered two major limitations. First, no routine measurements were taken before 1951, so that the assignment of exposure categories for men employed between 1933 and 1950 was less firmly based. There were few major process changes between these dates and most earlier jobs could be assigned 1951–55 exposure levels with reasonable confidence. In some areas, however, conditions had improved and a higher category (again at 1951–55 levels) was assigned for pre-1951 exposure. The second, and more important, difficulty was the absence of reliable data for the highest exposure levels. The highest measured levels in 1951–55 were recorded at two sampling points in the carding department (Fig. 5/1) but other jobs in areas where no samples were taken, including loading and stacking operations and work in a fibre warehouse, were known to involve very high exposure; these were arbitrarily assigned the average observed in the two highest carding levels in 1951–55. Conditions in carding had greatly improved by 1956, but no material change occurred in these other dusty areas and they were allocated the same (1951–55) level from 1933 to 1960.

The dust levels (in p.ml^{-1}) for each exposure category for the period 1951–60 were calculated by averaging the results for the corresponding sampling points, with the exception mentioned above of "very high" for the period 1956–60. The measurements (taken in f.ml^{-1}) since 1961 were, however, very much more variable in certain areas than the earlier particle counts and the sampling points were changed several times between 1961 and 1972. It was, therefore, difficult to select an appropriate set of sampling points that could be regarded as representative, particularly for the higher exposure levels. The levels assumed for different exposure categories for this period (from 20 f.ml^{-1} for "very high" to 2.5 f.ml^{-1} for "low") were chosen as an approximation to the averages for the jobs assigned to them, but they were not formally calculated.

We observed little or no excess risk before 20 years after first exposure and ignored exposure in the five years preceding death in all dose-response calculations. Our results are therefore dominated by the pre-1961 exposure estimates so that any error in more recent estimates or in their conversion to particle counts cannot have greatly influenced our dose-response analysis.

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Quebec chrysotile miners and millers

The Quebec data, which are the most extensive, began to be collected in 1949, two years before the Rochdale data, following a period in which the conditions had not greatly altered for many years. One important reservation is, again, the weakness of the exposure estimates in areas of high exposure. The high mortality rates observed in these areas have a strong influence on the overall dose-response analysis, but the corresponding measures of pollution were inadequately monitored. In all studies in which a clear dose-response relationship has been observed, the clarity of the relationship is largely due to the high lung cancer mortality rates associated with high exposures that were estimated for periods and areas in which little or no sampling was done.

The estimate of the dose-specific risk based on these data, as in other cohorts, is largely determined by the high relative risk among workers who were heavily exposed before the period when routine measurements were taken and is therefore of doubtful accuracy as an indicator of the risk under current working conditions. Moreover, there were no routine measurements in the open pits, and few in the underground mines, and the exposure estimates assigned to the substantial proportion of the cohort who worked in these areas may be particularly unreliable. The conversion of high particle counts to fibre counts is also difficult, as only 34 (5%) of the parallel samples shown in Fig. 4/1 exceeded 3 mppcf, and none exceeded 5 mppcf, while the estimated average exposure levels of men with 20 or more years' service ranged from 4.2 mppcf for "low" exposure to 46.8 mppcf for "very high" exposure (McDonald *et al*, 1980).

The observation that men with prolonged "low" exposure under conditions that were certainly dustier than those obtaining in the mines today suffered relatively low excess mortality is extremely useful for setting exposure limits for chrysotile asbestos mining. As in our own study, however, the lack of contemporary particle and fibre counts during the period when the exposures that caused the highest observed excess risks occurred, together with the poor correlation subsequently observed between particle and regulated fibre counts, make it impossible to quantify dose-specific effect at low fibre counts with much confidence.

Chrysotile textile manufacture in South Carolina

Workers at this factory were studied by Dement *et al* (1982) and independently by McDonald *et al* (1983a), the latter including a larger group of employees. The results, which were similar in both studies, are of particular interest, as they have provided one of the highest dose-specific estimates of risk for chrysotile exposure in a factory in which exposure levels were measured more than 30 years ago. The relative risk for lung cancer in the highest exposure category was of the order of 10 and the qualitative conclusion that the dose-specific increase in risk (per mppcf) was substantially higher than in chrysotile mining cannot reasonably be disputed. This is indicated in Fig. 5/2, which reproduces the different dose-response relationships that McDonald *et al* (1983a) obtained for the two processes. That the dose response relationships should be different is not, however, surprising as the hygiene measurements were made in terms of particles and the proportion that were asbestos fibres is likely to have been much greater in the textile factory than in the mines.

The exposure data obtained in the factory are less extensive than appears at first sight. A total of 5576 samples were taken before 1975, but only 376 midget impinger samples were taken before 1960, including 112 by a life insurance company and 81 by the US public health service or state board of health between 1930 and 1945. It is difficult to know how representative these were, and many activities, including fibre mixing with pitch forks in an area where there was no dust suppression, were unmonitored. The area in which estimated particle counts were highest was twisting and continuous exposure in this area from 1935 to 1970 at the levels assumed would have constituted a cumulative exposure of under 100 mppcf-years. In the dose-response analysis, however, a group is shown with a relative risk of about 10 whose estimated exposure already exceeded 120 mppcf-years by 45 years of age (Fig. 5/2; McDonald *et al*, 1983a). The estimates of risk must, therefore, have been strongly influenced by results for men in unmonitored areas whose exposure could only be guessed. A more detailed breakdown of these data by period of first exposure and duration of exposure would make it easier to assess the reliability of the

Other studies

A study conducted by McDonald *et al* (1983b) in a factory in Pennsylvania in which textiles and other asbestos products were manufactured gave an estimate of the dose-specific "respiratory cancer" risk almost identical to that for the South Carolina chrysotile textile plant just referred to. Some exposure data were available for the Pennsylvania factory from the 1930s, but they were not described as fully as those for the South Carolina. Moreover, the data are difficult to interpret because pleural mesotheliomas and lung cancers were combined in a single dose-response analysis and it is not clear what excess of lung cancer, if any, was observed.

Exposure conditions in the friction products factory, in which a mortality study was conducted by Berry and Newhouse (1983) were studied by Skidmore and Duffley (1983). These authors conducted an extensive simulation of pre-war working conditions; but they did not present details of the results (which were measured in $f.ml^{-1}$ by modern methods) and they merely classified each area and period in ranges (more than 20 $f.ml^{-1}$, 10–20 $f.ml^{-1}$, 5–10 $f.ml^{-1}$, etc). We also found it difficult to calculate average levels in $f.ml^{-1}$ due to the extreme variability of the results (Peto *et al*, 1985) and Skidmore and Duffley presumably summarised their results in this way for similar reasons. The study is, however, of considerable value as it showed little or no increase in lung cancer risk at any level of duration of exposure or of cumulative dose. It seems reasonable, therefore, to conclude that the risk in the friction products sector of the industury is likely to be low under modern conditions; but that the results may not provide useful risk estimates for other processes.

Several other studies have been used to provide dose-specific risk estimates. All but one of the estimates, have, however, been within the range spanned by those based on the studies discussed above and the exposure data on which they were based were less extensive (and in some cases non-existent). The exceptional risk estimate, and the highest so far published (Finkelstein, 1983) was based on an asbestos cement factory in which both chrysotile and crocidolite were used and exposures were not measured until 1969. The exposure estimates used, which Finkelstein "judged to be accurate within a factor of three or five" (on grounds which are not made clear) do not seem reliable enough to justify any quantitative conclusion.

Importance of individual exposure estimates

The highest observed relative risks for lung cancer have in the past been of the order of three to 10 in textiles, insulation manufacture and use, chrysotile mining and asbestos cement manufacture, and the only major sector of the asbestos industry in which the risk has been shown to have been consistently low for many years is the manufacture of friction products (Berry and Newhouse, 1983; McDonald *et al*, 1984). The gross differences between the dose-specific risk estimates calculated for different sectors are thus due

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more to differences between estimated exposures than to variation in the risks actually observed. The reliability of exposure estimates is therefore crucial to any comparison either of different sectors or of different studies within a sector. This cannot be assessed until the original measurements and the basis for particle to fibre conversion have been published in detail. As this has not been done, we have felt constrained to exclude other studies from further consideration, but we do not wish to imply that none of them can provide useful data.

Comparison of risk estimates

The differences between the estimated exposures and observed risks in chrysotile textile production, the manufacture of chrysotile friction products, and chrysotile mining are illustrated by the studies conducted by the same research team and analysed by similar methods (McDonald *et al*, 1983a; McDonald *et al*, 1984; McDonald *et al*, 1980). These authors conclude, as we do, that the differences are too marked to be attributable to chance or bias, and are likely to reflect systematic differences in fibre dimension that are not reflected in conventional fibre counts.

One outstanding anomaly which cannot readily be explained in this way is the apparently marked difference between our results and those obtained in an apparently similar factory in South Carolina (McDonald *et al*, 1983a). The dose-specific risk estimate for lung cancer in this factory, which was compatible with that previously derived by Dement *et al* (1982) from a smaller study in the same plant, was an increase in SMR of 0.075 per mppcf-year. The corresponding predicted cumulative dose at which the SMR would be doubled is 13.3 mppcf-years.

For the reasons discussed previously (see p. 5/16 *et seq.* and Peto *et al*, 1985), we believe that the increased SMR in men with low exposure at Rochdale may be an artefact, and we therefore calculated the increase in the SMR, constrained to equal unity at zero dose. The resulting estimate for all men first employed in 1933 or later was

$$SMR = 1.0 + 0.0054 \times \text{mppcf-years}$$

and for men first employed in 1951 or later

$$SMR = 1.0 + 0.0150 \times \text{mppcf-years}.$$

Possible reasons for this difference between men first exposed before and after 1951, which is statistically significant ($P<0.05$), are discussed in Peto *et al* (1985). Both estimates seem at first sight incompatible with those obtained by McDonald *et al*, but our exposures were measured with a thermal precipitator, while theirs were measured with a midget impinger and the different instruments must be expected to give different results as was discussed in Chapter 4. An idea of the appropriate conversion factor is provided by the comparisons of particle and fibre counts in the two factories. We observed an average ratio of approximately 1 $f.ml^{-1}$ per mppcf. The corresponding ratio in the South Carolina plant was about 3 $f.ml^{-1}$ per mppcf in most areas and 8 $f.ml^{-1}$ per mppcf in preparation areas according to Dement *et al* (1982), while McDonald *et al* (1983a) suggested an overall average of about six. The dose-specific risk estimates based on midget impinger counts should therefore be reduced, perhaps by a factor of six leading to an increase in SMR of 0.0125 per mppcf-year, to correspond to our estimates based on thermal precipitator counts. Such an adjustment would make our estimate based on men first employed in 1951 or later slightly higher than that reported by McDonald *et al*, although our overall estimate would still be rather lower. In view of the uncertainties in such conversion the surprisingly close correspondence between these adjusted estimates is perhaps fortuitous, but the results of the two studies are certainly compatible.

Preferred estimate

The best estimate we can make of the dose-response relationship for lung cancer that occurs in chrysotile textile workers is, therefore, something intermediate between that observed in Rochdale (using a conversion factor of 1 mppcf = 1 $f.ml^{-1}$, see p. 4/26) and the roughly similar relationship observed in South Carolina (using the conversion factor of 1 mppcf = 6 $f.ml^{-1}$ suggested by McDonald *et al*, 1983a). This we suggest should be taken as:

$$SMR = 1.0 + 0.01 \text{ } f.ml^{-1}\text{-years}.$$

This is intermediate between our estimates for workers first employed in the Rochdale factory between 1933 and 1950 and between 1951 and 1974 and is close to the estimate based on the SMR or on the size of the risk relative to that in men with low exposure in the South Carolina factory (McDonald *et al*, 1983a). In view of the many reservations that must be made concerning such extrapolations, we prefer to express the relationship in round figures. The calculations that will be made in Chapter 6 will, therefore, be based on the above formula, rather than on an exact relationship derived (after making many assumptions) from any one study.

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Table 5/1 Mortality from asbestosis in asbestos textile workers (followed to 30.06.83, see Peto *et al*, 1985)

Sex	Period since first employed (years)	Annual death rate per 1000 persons					
		employed 20 years or more in scheduled areas: first employed		employed 5* years or more in scheduled areas: first employed		employed less than 5 years in scheduled areas: first employed	
		10 or more before 1933	some, but less than 10 before 1933	1933–50	1951–74	1933–50	1951–74
M	5–19	—	—	0.4 (3/8520)	0.0 (0/4814)	0.0 (0/1355)	0.0 (0/12918)
	20–29	6.5 (3/464)†	1.8 (1/552)	0.2 (1/4791)	0.0 (0/1806)	0.0 (0/6090)	0.0 (0/3557)
	30 or more	10.9 (6/552)	5.0 (5/1003)	0.9 (3/3297)	0.0 (0/94)	0.0 (0/3941)	0.0 (0/150)
	all periods	8.9 (9/1016)	3.9 (6/1555)	0.4 (7/16608)	0.0 (0/6714)	0.0 (0/25216)‡	0.0 (0/21325)‡
F	10–19	—	—	0.0 (0/1424)	0.0 (0/791)	—	—
	20–29	—	—	0.0 (0/1652)	0.0 (0/534)	—	—
	30 or more	—	—	0.6 (1/1725)	0.0 (0/25)	—	—
	all periods	—	—	0.2 (1/4801)	0.0 (0/1350)	—	—

* Women employed for 10 years or more in scheduled areas.
† Number of deaths and person-years at risk in parentheses.
‡ Including person-years at risk less than 5 years since first employment.

Note to Table 5/1

Five men, who were first employed after the end of 1932, are also known to have died of asbestosis. They were excluded from the cohort studied for reasons given by Peto *et al* (1985). Their employment histories were:

(i) Occupationally exposed to asbestos elsewhere for 1 year before employment in Rochdale 1937–42 and 1946–60 (scheduled areas throughout). Died 1969, aged 51 years.

(ii) Occupationally exposed to asbestos elsewhere for 30 years before employment in Rochdale 1940–47 (scheduled areas 1 year). Died 1967, aged 73 years.

(iii) Occupationally exposed to asbestos elsewhere for 1 year before employment in Rochdale 1948–65 (scheduled areas 13 years). Died 1971, aged 71 years.

(iv) Employed Rochdale 1948–57 (scheduled areas throughout), subsequently transferred to Hindley Green factory with further exposure (1957–61). Died 1971, aged 54 years.

(v) Employed Rochdale 1937 (6 months), 1939–41, 1946–49 (scheduled areas throughout). Name erroneously omitted from register of employees. Died 1974, aged 62 years.

None were first employed after 1950.

Table 5/2 Mesothelioma mortality among men first employed in 1933 or later in a chrysotile textile factory in Rochdale. Observed deaths (O) and man years (MY) (Peto *et al*, 1985)

Years since first employment	*Duration of scheduled service (years)*													
	Less than 1 yr		*1–4 yrs*		*5–9 yrs*		*10–19 yrs*		*20–29 yrs*		*30 yrs or more*		*Total*	
	O	*MY*	*O*	*MY*	*O*	*MY*	*O*	*MY*	*O*	*MY*	*O*	*MY*	*O*	*MY*
0–19	1*	28 015.0	0	4785.6	0	8520.5	0	4814.1	—	—	—	—	1	46135.1
20–24	0	4668.2	0	877.4	0	1416.8	0	1423.3	1	848.3	—	—	1	9234.1
25–29	0	3469.8	0	631.7	0	1103.5	0	869.7	1	935.3	—	—	1	7010.0
30–34	0	2041.2	0	421.3	0	707.2	3	469.7	2	599.7	0	86.2	5	4325.3
35–39	0	840.4	0	237.7	0	383.3	0	204.0	1	257.1	0	106.9	1	2029.4
40 or more	0	402.3	1	148.4	0	249.1	1	102.3	0	121.7	0	103.4	2	1127.3
All periods	1	39436.9	1	7102.0	0	12380.4	4	7883.0	5	2762.2	0	296.6	11	69061.1

* This case in a man who was exposed for 4 months and died from "endothelioma of the pleura" 4 years later in 1950 was excluded from the risk calculation, as the tumour seemed unlikely to have been caused by exposure at Rochdale (see original report).

Table 5/3 Observed (O) and expected (E) numbers of lung cancer deaths among men first employed in 1933 or later in a chrysotile textile factory in Rochdale (Peto *et al*, 1985)

	Years since first exposure	*Duration of service in scheduled areas*											
		Less than 1 yr		*1–4 yrs*		*5–9 yrs*		*10–19 yrs*		*20 yrs or more*		*Total*	
		O	*E*	*O*	*E*	*O*	*E*	*O*	*E*	*O*	*E*	*O*	*E*
First exposed 1933–50	0–19	13	8.75	1	1.86	6	4.70	5	4.31		—	25	19.62
	20–34	22	16.55	4	3.55	8	7.09	15	5.90	9	6.05	58	39.14
	35+	9	5.22	0	1.60	3	2.94	0	1.39	4	2.91	16	14.06
	Total	44	30.51	5	7.01	17	14.73	20	11.60	13	8.95	99	72.81
First exposed 1951–74	0–19	7	8.74	1	1.88	2	3.31	4	2.35		—	14	16.28
	20–32	6	5.72	1	0.96	0	1.81	8	1.83	4	1.05	19	11.37
	Total	13	14.46	2	2.84	2	5.12	12	4.18	4	1.05	33	27.65
All men	0–19	20	17.49	2	3.74	8	8.01	9	6.66		—	39	35.90
	20–34	28	22.27	5	4.51	8	8.90	23	7.73	13	7.10	77	50.51
	35+	9	5.22	0	1.60	3	2.94	0	1.39	4	2.91	16	14.06
	Total	57	44.97	7	9.85	19	19.85	32	15.78	17	10.00	132	100.46

Table 5/4 Ratio of observed to expected lung cancer mortality in amosite workers
(Numbers of deaths and expected numbers in parentheses)

Duration of exposure	*Age at first exposure*	*Median age*[a] 40	50	60
Under 9 months	15–	6.85 (1/0.15)	2.73 (2/0.73)	
	25–	0.00 (0/0.14)	4.27 (3/0.70)	4.03 (6/1.49)
	35–		3.75 (2/0.53)	2.91 (4/1.37)
	45 or over			0.00 (0/1.11)
9 months or more	15–	19.07 (2/0.10)	13.13 (6/0.46)	
	25–	0.00 (0/0.09)	11.45 (5/0.44)	7.41 (8/1.08)
	35–		11.94 (4/0.34)	5.62 (5/0.89)
	45 or over			9.93 (8/0.81)

[a] The data, which were presented in decades of time since first exposure (5–14, 15–24, 25–34), are tabulated by the corresponding medians of age. Expected numbers were calculated approximately by Walker (1984) from the data published by Seidman *et al* (1979).

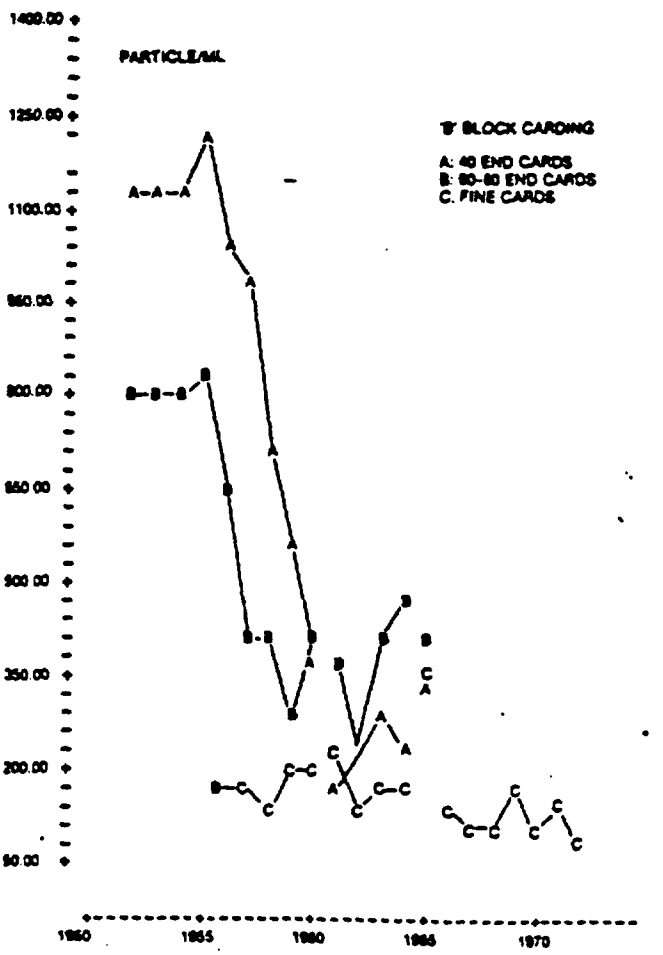

Fig. 5/1 Amount of asbestos in the Rochdale factory air in million particles per cubic foot (mppcf) averaged over each year from 1952 to 1972 and three sampling points in the carding area: measurements in f.ml^{-1} from 1961 regarded as equivalent to mppcf (see text). Reproduced from McDonald *et al*, 1983a, with the permission of the authors and the editor of the British Journal of Industrial Medicine.

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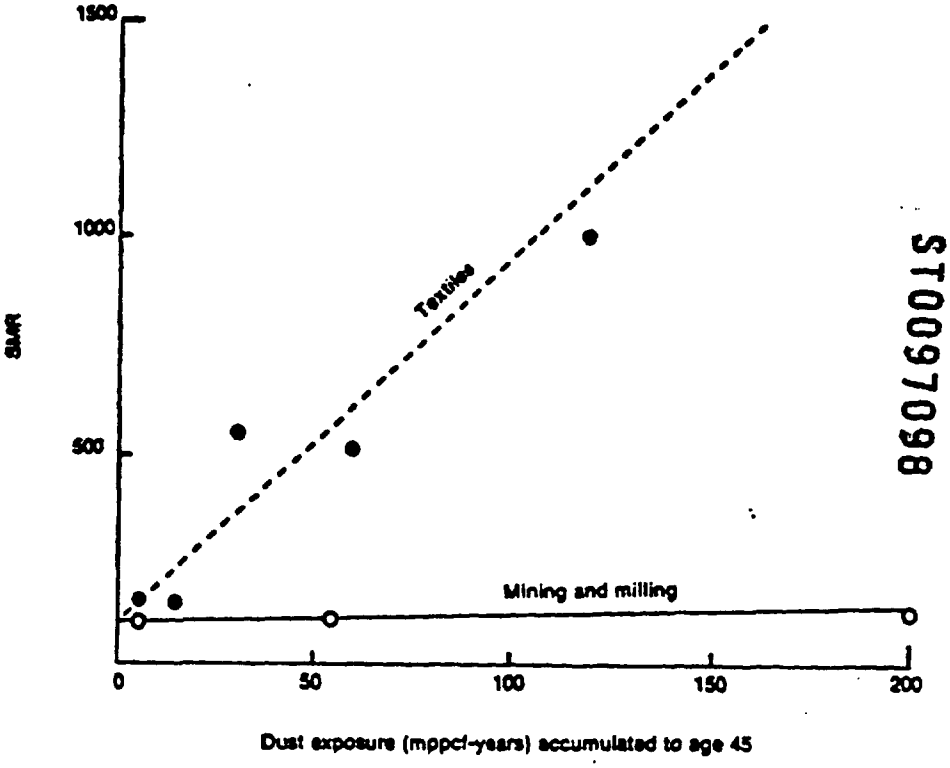
Fig. 5/2 Respiratory cancer SMRs in relation to dust exposure accumulated to age 45 in chrysotile mining and milling, and in chrysotile textile manufacture (McDonald *et al.*, 1983a).



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6 Effects anticipated with current control limits

In Chapters 4 and 5, we have expressed serious doubts about the comparability of the measures of pollution that have been made in the past and the possibility of relating them in any meaningful way to the epidemiological observations that have been made on asbestos workers. It might therefore be thought that none of the data that have been collected permit any truly scientific prediction of the likely effects of the limits to exposure that have now been set. This may, indeed, be the case. Decisions, however, have to be made and, despite the lack of clarity of the results, it is certainly possible to use them to draw some conclusions.

Amphibole asbestos

The use of crocidolite and amosite (and, we assume, of other types of amphibole asbestos) is, in practice, more hazardous than the use of chrysotile possibly because of the longer residence time of amphibole fibres in the lungs, but possibly also for other reasons relating to the configuration of the fibres most commonly encountered. No worthwhile data are, however, available to enable quantitative comparisons to be made between the effects on humans of the different types of fibre. It can be concluded only that the use of amphiboles should be avoided whenever possible and that extra precautions need to be taken when exposure to them occurs. It is possible, though we believe unlikely, that the hazardous effects of chrysotile are mainly due to contamination with small amounts of tremolite; but this is of no practical interest to users of chrysotile, unless it is possible to obtain supplies in which the small amounts of tremolite are substantially reduced.

Dose-specific risk estimates for chrysotile textile production

The data on chrysotile textile workers can be used to provide a broad indication of the risk that is likely to be entailed by the maximum intensity of exposure that is now permitted. No precise prediction is possible, however, because: (a) no biological models for the production of cancer have been established; and (b) no precise comparisons can be made between the extent of past and current exposure.

In areas where the average level exceeds 0.5 f.ml^{-1} (the control limit for chrysotile asbestos now in force in Britain) the regulations stipulate that respirators must be worn. If these regulations are stringently enforced, the average level of exposure will be lower than the permitted maximum, perhaps substantially so. We have therefore calculated the effects of exposure at an average level of 0.25 f.ml^{-1}, which is half the control limit and is probably more representative of the consequently show the risks calculated on this basis in Table 6/1. If, however, any workers are consistently exposed to an average level close to 0.5 f.ml^{-1}, the predicted risks would, of course, be doubled.

In calculating these risks we have used the formulae derived in Chapter 5 which are the best estimates we can make of the separate dose-response relationships for lung cancer and for mesothelioma, derived from the available British and American data. The data do not allow any estimate to be made at all precisely and the estimates made in Chapter 5, it will have been noted, were deliberately rounded off.

The predicted risks for lung cancer and mesothelioma for men first exposed at various ages and for different periods at a constant level of 0.25 f.ml^{-1} that are shown in Table 6/1 are calculated from current national lung cancer and total mortality rates and thus describe a mixed population including both smokers and non-smokers. The predicted risk to a man who began work at age 20 years and was exposed at an average level of 0.25 f.ml^{-1} is approximately 0.4% for 15 years' employment and 0.8% for 35 years' employment, while a man who began work later in life would experience risks that were somewhat smaller. The risks for lung cancer will however be substantially less than those shown in Table 6/1 if the recent dramatic fall in lung cancer mortality in men under 50 years of age (now less than half what it was 25 years ago) extends into older ages as the effect of a reduced prevalence of cigarette smoking and reduced tar content of cigarette smoke continues to make itself felt. Similar calculations for women would show slightly higher mesothelioma risks, because of their longer life-expectancy, and lower lung cancer risks, because women smoke less than men. Lung cancer rates in older women are still rising sharply due to past changes in cigarette smoking, however, and young women now smoke almost as much as men. If these trends continue, the eventual lung cancer risk to women may approach that among men. The predicted risks to both smokers and non-smokers of either sex would be similar to those shown in Table 6/1 for mesothelioma and, among non-smokers, less than 10% of those shown for lung cancer, while for smokers the lung cancer risks would be increased by about 50%. We have not tabulated separate sex- and smoking-specific predictions, however, as such detailed calculations would lend a spurious air of precision to estimates that are necessarily approximate. The predicted risks do, however, conform to the qualitative results of direct observation in relation to the effect of age at first exposure. The risk of mesothelioma is very much higher when exposure occurs early in life, but the lung cancer risk is hardly affected.

The predicted ratios of mesothelioma to excess lung cancer shown in Table 6/1 are probably compatible (statistically) with that observed in South Carolina and

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quoted, although to test this formally would require more detailed information than has so far been published on these two cohorts. This consistency with the only published cohorts exposed almost exclusively to chrysotile in which substantial increases in risk were observed has been achieved by assuming: (a) that half of the mesotheliomas that occurred in men first employed in 1933 or later at Rochdale were caused by crocidolite; and (b) that the absence of any cases of pleural mesothelioma in the South Carolina plant was a chance occurrence (see Chapter 5). We recognise, however, that the ratio of mesothelioma to excess lung cancer may well depend on the way that asbestos is processed as well as on fibre type and we are not sure whether Table 6/1 constitutes an average of similar measurements or an uneasy compromise between fundamentally different disease patterns.

The predictions shown in Table 6/1 are based on rather complex models, but similar figures can be calculated very much more simply from the raw data. In our study, for example, the combined excess of lung cancer and mesothelioma beyond 20 years after first exposure in men exposed for more than 10 years in scheduled areas was 17% (29.87/175.87) of the expected number of deaths from all causes (Peto *et al*, 1985). This excess was caused by exposures at an average level of the order of 10 f.ml^{-1} for durations averaging about 20 years, and a similar duration of exposure at 0.25 f.ml^{-1} would (assuming linear dose-response) therefore have increased total mortality by about 0.43%. If, as our models predict, this proportional excess will remain roughly constant during further follow-up, the corresponding lifelong risk would also be about 0.43%, or about one in 240.

This simple calculation highlights the crucial importance of the assumption that the risk will be reduced in direct proportion to the reduction in fibre counts that we presume have occurred. Uncertainty about the relative effects of varying duration of exposure and of the extent to which the risks persist into old age are of secondary importance.

Particle and fibre counts as indices of risk reduction

All measurements taken prior to the advent of electron microscopy are indirect, as many of the most carcinogenic fibres were probably not counted, and any extrapolation from either particle or regulated fibre counts is based on the implicit assumption that the most dangerous fibres constitute more or less the same proportion of all airborne particles counted under current working conditions as they did in the past. There are two ways in which this can be tested. The first is to continue observation of cohorts such as our own, which is certainly worthwhile but cannot provide much useful information relating to current exposure levels for many years. The second is by more precise analysis of the distribution of fibre sizes in modern factories and under the conditions that obtained in the past, which could be studied only by extensive simulation of earlier work practices. Quantitative interpretation of such a comparison would also require detailed information on the dependence of both carcinogenicity and pulmonary and bronchial retention on fibre dimension; but if it could be shown that exposure to long fine fibres had consistently fallen by at least as much as the numbers of particles or fibres that have been counted, such sophisticated analysis might not be necessary.

The limited comparisons of fibre dimensions that have already been published indicate that differences between the observed risks in mining friction product manufacture, and textile production may be entirely explicable in these terms, and similar studies in areas of asbestos manufacture and use that have not been adequately studied epidemiologically might give a useful indication of their likely hazard. The continued use of regulated fibre counts based solely on optical microscopy to compare grossly different situations such as buildings containing asbestos insulation and factories in which asbestos textiles are manufactured is scientifically indefensible in the absence of such data.

The high relative risk for lung cancer in our own study among men first exposed in 1951 or later, in spite of the reduction in particle counts that occurred between 1951 and 1960, may, we concluded, have been inflated by chance but it certainly suggests that the carcinogenic effect of the exposure may not have fallen as much as the measured levels would imply.

Other possible sources of error in predicted risks

The possibility that the carcinogenic effect is not adequately measured by past particle or regulated fibre counts is the principal objection to the risk estimates that we have calculated, but there are several other possible sources of error. We have not attempted to estimate and correct for them, however, as their effects are so uncertain that it is almost impossible to do so objectively.

Models of cancer risk

There is quite strong evidence that the relative risk for lung cancer eventually falls after exposure to asbestos has ceased. Such a reduction has been consistently observed following quite heavy exposure, and the only grounds for not including it in our model are: (a) that the effect might be less marked following less intense exposure; and (b) that there are not sufficient data to estimate either the time when it occurs or its magnitude with much confidence. Other aspects of the models for both lung cancer and mesothelioma are also open to serious doubt but it is not clear whether any resulting errors are likely to have increased or reduced our risk estimates.

Comparability of measurements

The effects of the introduction of the microscope eyepiece graticule, which tends on average to increase the fibre count (Beckett *et al*, 1976), should perhaps have been allowed for in our conversion of early measurements to modern fibre counts. We did not do so, however, as the appropriate conversion factor

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varies between observers and fibre types, and perhaps also with intensity of exposure. For example, the factor of under 1.2 reported by Skidmore and Difficy (1983) for counts "at the time of changeover" for friction materials is considerably lower than the range of two to three quoted by Acheson and Gardner (1979). The effect of changing from static to personal sampling is also difficult to assess. Routine measurements taken in the Rochdale factory suggest that personal measurements were consistently lower than static ones in 1971, although subsequent studies at lower dust levels suggest the opposite. As we wish to ascertain the personal readings that would have been obtained in the past the earlier results would seem more relevant; but it would not be reasonable to increase our risk estimates to allow for this effect without also reducing them to compensate for the change in counting, which, in the Rochdale factory, may well have had an approximately equal and opposite effect.

The confounding effects of crocidolite

For the reasons discussed in Chapter 5 we believe that some of the mesotheliomas that occurred in the Rochdale factory were caused by crocidolite, and we have reduced our risk estimate for mesothelioma to allow for this. Exposure to crocidolite may, however, also have caused part of the observed excess of lung cancer and this has not been allowed for. The ratio of numbers of mesotheliomas to the excess of lung cancer has varied erratically in different studies and, according to Berry and Newhouse (1983) occasional crocidolite exposure may increase the risk for mesothelioma more than for lung cancer. It was, therefore, difficult to decide what corresponding figure to use. The effect would, in any case, have been only marginal and would not have had any effect on the rounded off estimate derived from combining our data with those of McDonald *et al* (1983a).

The control limit for chrysotile

Textile manufacture

We are left, therefore, with a central estimate of the lifelong risk caused by 20 to 30 years' exposure in chrysotile textile manufacture of the order of 0.5% for exposure at an average concentration of 0.25 f.ml^{-1}, which we believe is a reasonable estimate of the conditions that will prevail when the current control limit of 0.5 f.ml^{-1} is enforced. This corresponds to a loss of expected life of only about one month when averaged over the whole workforce and the loss of about 12 years of expected life for the unfortunate individuals who die of asbestos-induced disease. There are many uncertainties underlying this prediction, and there are several grounds for suspecting that it may be too high (the contribution of crocidolite; the possibility that the highest exposures were underestimated; the [illegible] and the evidence that

On the other hand, our observations on men first employed since 1950 at Rochdale gave a slightly higher risk estimate for lung cancer than the overall figure that we have assumed, and the exposure of this subgroup was probably measured more reliably than that of any other comparable cohort. The only further qualification that should be taken into account in considering these predictions is that they refer to an average concentration of 0.25 f.ml^{-1}. If the average concentration is maintained above or below this level, irrespective of occasional peaks, the risks will of course also be increased or reduced accordingly.

Other sectors of the asbestos industry

The hazards associated with different branches of the industry are different; not only because of differences in the concentration of asbestos fibres in the air, but also because the configurations of the fibres differ as a result of the different treatments they have received. As the biological effects of asbestos are crucially dependent on the configuration of the fibres, a standard control limit that is defined solely by numbers of fibres with a wide range of sizes is likely to result in differing standards of risk. Mines are a rule to themselves and we cannot use experience in them to control the limits of exposure in manufacturing or construction industries, except in so far as it provides evidence of the type of biological effect that exposures to different mineralogical types of the material are likely to produce.

Within industry, the most hazardous type of occupation is insulation work, the workers in which may have been exposed to appreciable amounts of amphibole asbestos. This conclusion is confirmed by the preliminary results of the Health and Safety Executive's national asbestos survey. Among men observed 10 or more years after first employment, the proportion of deaths attributed to mesothelioma was 11.3% (based on 17 cases) and the standardised mortality ratio for lung cancer was 3.11 (43 observed deaths and 13.8 expected) against a proportion of 2.4% (also based on 17 cases) and an SMR of 1.11 (110 observed deaths and 99.4 expected) for all employees in the other nine industrial groups covered by the survey. No figures are available to quantify at all accurately the intensity of the pollution to which insulation workers have been exposed nor can any subgroup be defined that has been exposed only to chrysotile. Special measures are certainly required to limit exposure to work of this type as has been recognised in the code of practice for work with asbestos insulation (Health and Safety Commission, revised February 1985).

Friction product workers, by contrast, have experienced very little risk, possibly because of the configuration of the fibres to which they are exposed, and control limits that are thought appropriate for textile workers should ensure an appreciably lower risk than textile workers would be expected to incur. The

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observed only in asbestos-cement workers exposed to crocidolite as well as to chrysotile, but data on pure chrysotile exposure are too limited to justify any firm conclusion. The Ontario Royal Commission (1984) inferred that the risk was low, and probably of the same order as in friction products manufacture; but we would question their observation that "the Weill study of New Orleans asbestos-cement plants discovered no excess risk of respiratory malignancy among those workers not exposed to crocidolite". The relative risk in this subgroup increased progressively and significantly with cumulative dose (Weill *et al*, 1979), and both the low relative risk in the lowest exposure category and the failure to observe a significant excess in the highest may have been due to the incompleteness of follow-up (which was substantial) or to the use of inappropriate rates in the calculation of expected numbers. The relative risk in men with cumulative doses exceeding 16.7 mppcf-years was more than three times that in the lowest exposure group (eight observed, 4.4 expected compared with 12 observed, 21.4 expected), and we can only endorse Acheson and Gardner's (1983) conclusion that "the manufacture of asbestos cement products from chrysotile may have been associated with relatively little excess mortality, but more information is urgently needed on this point".

Asbestos in buildings

Estimation of the effect of environmental exposure in buildings is still more complex than estimation of the effect at work. For it not only requires extrapolation over several more orders of magnitude, with all the biological uncertainties that that involves, but it also depends on measures of exposure that are still less reliable. Pollution measurements made in terms of the mass of asbestos per cubic metre of air are practically meaningless, as we do not know what proportion of the mass is composed of fibres of carcinogenic size and counts of "regulated fibres" per ml that are made by optical microscopy are not much better, as they invariably include many non-asbestos fibres from other sources. At the very low levels that are encountered, only measurements of fibres that have been identified as asbestos by transmission electron microscopy (TEM) are of any value. These are complicated by the need to convert to "regulated fibres" counted by the optical microscope, as it is only for the latter fibres that we have any corresponding measures of risk. This, however, is not a serious problem as counts in two asbestos textile factories suggest that the optical count is approximately half that of the TEM count (Dement and Harris, 1979; Rood and Streeter, 1984).

Very few measurements have yet been made by transmission electron microscopy of general atmospheric pollution within buildings and many of these have failed to detect any asbestos fibres of the relevant sizes. When the Ontario Royal Commission (1984) sought to estimate the effect that exposure within buildings might have they postulated possible exposures of the order of 0.001 f.ml^{-1} (as determined by optical microscopy) and calculated that a man who worked in such a building for 10 years "might face a risk of death from that 10 year exposure of 20 per million. If the same person drove 10 miles to and from the building 250 days per year for 10 years ... the risk of death from commuting [would be] 1125 per million. In short, the drive is over 50 times as dangerous as the building occupancy." The estimate of the effect of asbestos is, however, likely to be on the high side for the Royal Commission pointed out that the postulated concentration of 0.001 f.ml^{-1} was an upper limit for most asbestos-containing buildings, while our review suggests that the postulated life-time risk of death from such a concentration of chrysotile fibres should be halved. The review of published studies by the Ontario Royal Commission and the results of measurements made in British buildings on behalf of the Department of the Environment suggest that exposure to true asbestos fibres of regulated sizes within asbestos-containing buildings is seldom more than 0.0005 f.ml^{-1} above background (expressed as an optical count derived by halving the TEM count). From Table 6/1 it can be calculated that exposure to this amount for 40 hours a week for 20 years would produce a life-time risk of approximately one per 100,000, while the risk for longer periods of exposure would be proportionately greater.

It is difficult to convey any meaning, in terms of ordinary experience, to life-time risks of the order of one per 100 000 and a Royal Society (1983) study group suggested that such risks could perhaps be classed as negligible. The Ontario Royal Commission tried to convey the meaning by making a comparison with the risk of driving to work. The risk can also be compared with that from exposure to tobacco smoke that other people produce. The amount of smoke inhaled in this way has been estimated to be on average, in the US, the equivalent of smoking one tenth of a cigarette a day (Repace and Lowrey, 1984), and a similar figure has been obtained by Wald *et al* (1984) in Britain for non-smokers who are exposed to smoke at home or at work for more than seven hours a week. Smoking at this level is estimated to produce a life-time risk of lung cancer alone of about 90 per 100 000; that is nearly two orders of magnitude more than the risk from exposure to asbestos in buildings of the sort that was cited above.

The actual number of deaths caused by such exposure cannot be calculated without national data on the proportion of the population that live or work in contaminated buildings and the average asbestos levels that they are exposed to, but the method can be illustrated with hypothetical figures. Suppose, for example, that 20% of the population suffer an exposure causing an average risk of one in 100 000. This could be due to 20 years' exposure in an office at 0.0005 f.ml^{-1}, to 10 or so years' exposure at school at a similar level (allowing for the increased mesothelioma risk caused by early exposure); or to more prolonged exposure at home at a lower average level. Such

exposure would cause approximately one death per year in the whole country. This effect, it must be emphasised, has been estimated from the predicted risks for exposure to chrysotile and exposure to crocidolite (and possibly also to amosite) must be expected to produce effects that are appreciably greater.

Table 6/1 Predicted numbers of asbestos-induced deaths due to lung cancer and mesothelioma occurring before age 80 years among 1000 men in chrysotile textile manufacture exposed to a level of 0.25 f.ml^{-1}.
(Based on England and Wales male death rates in 1981–82 for lung cancer and all causes)

Age at first exposure (years)		Duration of exposure (years)			
		5	15	25	35
20	lung cancer	0.93	2.79	4.62	6.29
	mesothelioma	0.53	1.12	1.34	1.40
30	lung cancer	0.94	2.79	4.48	5.66
	mesothelioma	0.23	0.46	0.53	0.54
40	lung cancer	0.93	2.64	3.85	4.24
	mesothelioma	0.08	0.15	0.16	0.17

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7 Summary

Chapter 1

Our review of the adverse effects of asbestos on health concentrates on the ill effects of exposure at work and includes only a brief section on the effects produced in other circumstances.

Well established facts are described in outline and by reference to other reviews. Three controversial aspects of the problem are dealt with in detail:

(a) the types of cancer other than lung cancer and mesothelioma that can be produced by inhalation of asbestos fibres;
(b) the difficulties involved in assessing the quantitative effects of exposure; and
(c) the quantitative evidence relating the intensity and duration of exposure to the effects observed.

Chapter 2

Exposure to asbestos can lead to asbestosis, lung cancer, and mesothelioma and to several other conditions that are seldom of serious import (pleural effusions, diffuse pleural thickening, and pleural plaques). These last are not considered further.

Asbestosis

The signs and symptoms attributable to asbestosis (that is, fibrosis of the lungs caused by asbestos) can be produced by other conditions and diagnosis during life is a matter of judgment. It is seldom difficult with advanced disease and a clear history, but may be difficult otherwise, as there is no sharp point at which a change in state from healthy to diseased can be said to have occurred.

Asbestosis develops slowly and even the gross exposure of the past seldom caused death in less than 10 years. With decreased exposure no person with otherwise healthy lungs should die of it. In the presence of other diseases the marginal effects of minor fibrosis may aggravate symptoms and hasten death.

Lung cancer and mesothelioma

Lung cancers due to asbestos are indistinguishable from lung cancers due to other causes. They occur proportionately to the same extent in smokers and non-smokers. It follows, therefore, that: (a) smoking habits are irrelevant in determining cause; and (b) an individual who smokes and has been exposed to asbestos can materially reduce his risk by stopping smoking.

Lung cancer attributable to asbestos usually occurs more than 10 years after first exposure. The risk can be reduced by reducing exposure, but there is not thought to be a threshold dose below which no risk is produced.

Mesotheliomas occur in the pleura or peritoneum and most are attributable to asbestos. When caused by asbestos, they seldom occur within 15 years of first exposure and possibly never within 10 years. The risk is unaffected by smoking, but varies with the amount and type of asbestos to which exposure occurs.

The ratio of the number of mesotheliomas to the number of lung cancers produced by asbestos varies in different circumstances from about one to 10 to more than one to one.

Chapter 3

Gastro-intestinal cancer

Suspicion that asbestos might cause gastro-intestinal cancer was raised by a study of American insulation workers.

The results of 16 other studies have been analysed in which:

(a) standardised mortality ratios (SMRs) were recorded separately for lung, gastro-intestinal, and other types of cancer;
(b) there was evidence of a hazard of occupational cancer; and
(c) it was possible to separate the deaths attributed to mesothelioma from those attributed to other cancers.

The correlation between the SMRs for lung cancer and gastro-intestinal cancer was close ($r = 0.916$) and the relative risk attributed to gastro-intestinal cancer was generally about 20% of the corresponding excess for lung cancer. The correlation between the SMRs for lung cancer and other (non-gastro-intestinal) cancers was slightly less close ($r = 0.804$) and the excess relative risk attributed to other cancers was about 17% of the excess for cancer of the lung.

These findings could arise because asbestos is a cause of cancer in practically every organ or because some of the deaths due to lung cancer or mesothelioma are miscertified as due to cancer of other types. Miscertification has occurred often in the past, but it is difficult to interpret the results of studies in which special efforts were made to obtain the correct diagnosis after the deaths had been certified, as the numbers of deaths attributed to one particular type of cancer after review cannot be compared with the numbers expected from national mortality data based on death certificates.

Experiments have failed to produce gastro-intestinal cancer with asbestos in laboratory animals and critical examination of the evidence suggests that the excess mortality from gastro-intestinal cancer that has sometimes been observed is largely or wholly due to misdiagnosis of cancers of the lung and mesotheliomas of the pleura or peritoneum, except, perhaps, for the excess of cancer of the oesophagus.

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Laryngeal cancer

Many studies have reported an excess of laryngeal cancer. This is not likely to be due to miscertification and asbestos probably causes the disease. The relative risk is somewhat less than that for cancer of the lung and the absolute risk is much less.

Other cancers

Three out of five studies have found an increased mortality in asbestos workers from cancer of the ovary. The excesses observed could have been due to misdiagnosis.

Other studies have reported excess risks of cancer of the kidney and of large cell lymphomas of the oral cavity and gastro-intestinal tract, but the available data are too few for any conclusion to be drawn about their cause.

Chapter 4

Quantitative estimation of the effects of exposure is difficult because:

(a) asbestos is not a unique chemical but a family of compound chemicals with some useful mechanical properties in common;
(b) its biological effects are due in part to the physical configuration of its fibres;
(c) the proportion of fibres of any specific configuration varies with the mineralogical type and the way the asbestos is used;
(d) asbestos is encountered in company with other materials that may modify its effect;
(e) the methods of counting the fibres in air have varied over time and none accurately reflects the carcinogenic potential of the sample;
(f) early measurements of the ambient pollution were of particles that reflected only crudely and variably the number of fibres that are currently counted; and
(g) knowledge of the mechanism of human carcinogenesis is incomplete and it is not certain how best to measure quantitatively Man's biological response.

Laboratory evidence

Laboratory evidence suggests that the hazard is greatest with fibres between five and 100 μm in length and of less than 1.5 or 2 μm diameter. There are, however, no sharp boundaries between hazardous and non-hazardous configurations. Short fibres less than 1 or 2 μm in length may not be hazardous at all; but there is no evidence of any minimum diameter to hazardous fibres, which may be carcinogenic even when the diameter is so small that they cannot be seen by the optical microscope. Current regulatory standards which count fibres more than 5 μm long with aspect ratios of more than three to one (described subsequently as "regulated" fibres) may, therefore, not

All types of asbestos that have been used in industry produce pulmonary fibrosis, cancer of the lung, and mesothelioma in animal experiments and all produce these conditions with much the same frequency when the effects of equal numbers of fibres are compared.

Epidemiological evidence

Epidemiological evidence has little to contribute on the biological effects of fibres of different sizes. Differences in the distribution of fibres of different configurations may contribute to differences in risk for different industrial processes, but the data now available are too few and too inconsistent for any conclusions.

Other epidemiological evidence suggests that chrysotile:

(a) does not produce peritoneal mesotheliomas;
(b) produces both pleural mesotheliomas and lung cancers;
(c) produces relatively few mesotheliomas compared with lung cancers; and
(d) involves less risk than crocidolite (and probably less than amosite) of producing either.

The conclusion that chrysotile is carcinogenic to humans can be questioned only on the grounds that it is commonly contaminated by small amounts of tremolite (an amphibole). Any distinction between the effects of chrysotile and tremolite is, however, academic unless tremolite can be removed from chrysotile or supplies can be obtained that are tremolite-free.

Materials used in conjunction with asbestos may modify its effects and may contribute to the production of mesotheliomas of the peritoneum.

Measures of exposure

Very few measurements are available of the intensity of exposure to asbestos to which workers were subjected before 1950, when exposures were much greater than they are now. Since then a variety of instruments have been used. Early instruments counted particles, most of which were not fibres of asbestos, and different instruments with different capacities were used in different places.

Many years' study of the problem of converting measurements made in terms of particles into regulated fibres led McDonald to report to an Ontario Royal Commission (1984) that the problem might be "almost unanswerable".

It is concluded that:

(a) the relationship between the old particle counts and modern fibre counts has varied from place to place and from one level of pollution to another;
(b) the change to the graticule grid method of counting fibres has given different results in different hands and factors varying from one to two are appropriate for different sets of data;

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(c) the change from static to personal sampling has resulted in changes that are variable and sometimes large. No general rule for conversion is appropriate as the extent of the change has varied with the intensity of pollution; and
(d) the best estimate from the counts that have been made at Rochdale is that 1 mppcf converts to 1 f.ml^{-1}, which implies that about 3% of the particles were regulated fibres. This ignores the effect of changing to the grid graticule method of counting and to personal sampling from static.

Comparison between dose-specific estimates of risk obtained in North America and Britain are complicated by the use of different instruments to count particles. The results obtained can be compared only by comparing the various estimates of the factors required to convert from particles to regulated fibres.

Measures of response

Research is needed to determine how best to measure the biological response to asbestos. The difficulty in measuring the production of asbestosis derives from the difficulty in diagnosing objectively the onset of the disease. The difficulty with cancer is the need to make assumptions about the relative effects of varying the intensity and duration of exposure, of differences in the age at which exposure starts and stops, and of the extent to which asbestos fibres act synergistically with, or independently of, other carcinogenic agents.

Chapter 5

Asbestosis

The precautions already taken have virtually eliminated the gross disease that led to early death in the past. Lesser degrees of disease may, however, increase the death rate from other respiratory or circulatory disease, particularly as asbestos acts synergistically with smoking to produce non-malignant respiratory disease.

The best evidence relating non-fatal asbestosis to different levels of exposure is that considered in previous reports to the Commission. None has been obtained since to modify materially the conclusions previously reached. It is doubtful whether any practicable study would ever be able to demonstrate harmful effects from levels equal to or lower than 1 f.ml^{-1} per year.

It is concluded that there may well be a threshold below which the ratio of significant asbestosis to asbestos-induced cancer becomes zero or so low that asbestosis should be ignored in estimating the long term effects of exposure. This should be true for the fibre counts that are likely to occur in the future and the conclusion of the Ontario Royal Commission that "life time occupational exposure to asbestos ... in the range of 25 f/cc-years and below" cannot cause the fibrotic process to advance to the point of clinical manifestation is accepted.

Cancer

In spite of the many difficulties in formulating a model for the production of cancer, some model has to be adopted if estimates are to be made of the life-long effects of exposure to small amounts. The problem is simplified by combining intensity and duration of exposure in a single index of cumulative exposure. This, however, could lead to gross error if asbestos behaved like cigarette smoke and caused a greater effect by prolonging duration of exposure than by increasing intensity.

For both lung cancer and mesothelioma there is evidence that excess mortality is increased by more intense exposure, but it is insufficient to establish the form of the dose-response relationship. It is assumed that the increased risk of both diseases is directly proportional to intensity of exposure (dust level) but this is not demonstrably correct.

Fibre configuration, as well as fibre type, should be taken into account in formulating the models, but no useful data are available to enable it to be done.

Mesothelioma

Observation of many cases suggests that the incidence of mesothelioma at different times after first exposure can be described by the equation

$$\text{Incidence} = c.(\text{time since first exposure})^k,$$

where k is about 3 or 4 and c is determined by duration and intensity of exposure and probably also by the type of asbestos and the distribution of fibre sizes.

This model leads to the prediction that the risk will increase rapidly with continuous exposure up to 10 years, slowly with increasing exposure for 10–19 years, and hardly at all thereafter. The Rochdale data are consistent in showing little difference between exposure for 10 to 20 years and exposures of longer duration; this could be because the tissue burden of chrysotile is progressively reduced. Contrary to the common belief several studies show that brief exposures produce relatively little risk.

No reports of the dose-response relationship for mesothelioma have been published. The Rochdale data are consistent with a linear relationship, but the level of risk is likely to have been affected by the use of a small amount (2.6%) of crocidolite. No cases were observed in a chrysotile textile factory in South Carolina and the risk attributable to chrysotile is, therefore, postulated to be about half that actually observed at Rochdale.

Lung cancer

It is assumed that the relative risk of lung cancer from exposure to asbestos increases linearly during constant exposure, remains constant after exposure stops, increases in proportion to intensity of exposure, and is independent of age and smoking.

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Even under conditions of heavy exposure little if any risk is produced for at least five years and no increase in risk may be detectable for 15 or 20 years following prolonged exposure at lower levels. Exposure during the five years before death was, consequently, ignored in analysing the relationship between dose and response.

The relative risk was assumed to rise progressively with continuing exposure for at least 30 years. If it does not the assumption that it does will provide a further safety factor for any control limit affecting long-term workers, but may result in an underestimate of risk for short-term workers.

Observations on short-term workers have produced anomalous results, a disproportionately high risk having been observed in several studies of such workers exposed to asbestos or to other lung carcinogens. At Rochdale the excess risk in short-term workers was attributed to a combination of chance and selection bias, but such factors could not explain all the other observations. Other explanations include the possibility that short-term workers have been exposed to very high levels of dust that saturated the lungs. The peculiarities of the results on short-term workers deserve attention as a specific research problem, as the use of observations on them may, in some circumstances, distort estimated dose-response relationships. For present purposes it was concluded that long service workers should be compared with the local population or with men who have been exposed for one to five years.

Several sets of data show a substantial reduction in relative risk 35 or more years after first exposure. This may be because the elimination or inactivation of asbestos (particularly of chrysotile) progressively reduces the carcinogenic effect.

The available data on the synergism of cigarette smoke and asbestos suggest that the two agents multiply (or nearly multiply) each other's effects. Whether exact multiplication occurs is unimportant in practice, as the absolute risk to non-smokers is certainly small even after heavy exposure.

Several sets of data suggest that age at first exposure has no effect on the size of the eventual relative risk and this is assumed to be the case when the life-long risk of exposure is calculated.

The only studies for which detailed quantitative data are available over a considerable period and for which comparisons have been made of particle and fibre counts are those on chrysotile miners and millers in Quebec and chrysotile textile workers in South Carolina and Rochdale.

The Quebec data are in many ways similar to the Rochdale data; both include many measurements of environmental pollution dating back to 1949–51 but both suffer from the paucity of measurements in areas of high exposure. For both sets of data estimates of particles with counts of fibres are unreliable. The estimate of the dose-specific risk based on these data is largely determined by the high risk among workers who were heavily exposed before routine measurements were made and no parallel particle and fibre counts were made for such high pollution levels. The evidence that men with prolonged "low" exposure, under conditions that were certainly dustier than today, suffered a relatively small excess mortality is useful for setting exposure limits for chrysotile mining; but uncertainty about many of the essential facts makes it impossible to quantify the dose-specific effect of exposure at low fibre counts for other purposes.

Observations on the South Carolina textile manufacturers have provided the highest dose-specific estimate of risk for chrysotile exposure in a factory where exposure levels were measured more than 30 years ago, which is much greater than that observed in chrysotile mining. The exposure data for the period before 1960 are, however, questionably representative and the estimates of risk must have been strongly influenced by results for men in unmonitored areas.

Some observations on chrysotile friction product workers show no increase in lung cancer risk at any level of duration of exposure or of cumulative dose. The reason is not clear and the results do not provide useful risk estimates for other processes.

The exposure data from which other dose-specific estimates of risk have been derived are too imprecise to justify any quantitative conclusion.

The two sets of data that are most useful for obtaining a dose-response relationship for chrysotile are those derived for textile workers in South Carolina and Rochdale. The apparent differences between the relationships observed have probably arisen because of the use of different instruments to count particles. It is inappropriate to use a single factor to convert counts of particles to counts of regulated fibres for both studies. Internal evidence suggests that the factor for South Carolina should be about six times that for Rochdale. If this difference is allowed for, the two sets of results lead to broadly similar conclusions. In view of the many reservations that must be made about extrapolating from any of the available data, a rounded off estimate indicating a 1% increase in the standardised mortality ratio for lung cancer per year of exposure to one regulated fibre per ml is the best that can be suggested.

Chapter 8

The uncertainties that have been reviewed make it hazardous to predict the likely effects of the limits to exposure that have now been set. Nevertheless some conclusions can be drawn.

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Crocidolite and amosite are more hazardous than chrysotile and extra precautions need to be taken when exposure to them cannot be avoided.

Dose-specific risk estimates for chrysotile

The data on chrysotile textile workers provide a broad indication of the risk that is likely to be entailed by the maximum exposure currently permitted. These suggest that a man who begins work at 20 years of age and is exposed to an average level of 0.25 f.ml^{-1} (half the control limit currently in operation) will experience a risk of about 0.4% for 15 years' employment and 0.8% for 35 years' employment, while a man who begins work later in life will experience risks that are somewhat smaller. The actual risks can, however, be expected to be less as the reduced prevalence of cigarette smoking and the reduced tar delivery of the average cigarette should reduce the current risk of lung cancer.

Materially different risks must be expected for smokers and non-smokers and those for women will differ from those for men because of their longer life expectancy and different smoking habits.

All measurements of fibre counts before the introduction of electron microscopy provide indirect indications of risk, as any extrapolation from counts made by other methods requires the assumption that the most dangerous fibres constitute much the same proportion of all particles or fibres counted at each period. Continued observation of cohorts currently employed is, therefore, desirable.

The few comparisons that have been reported give grounds for believing that differences in the distribution of fibres of different dimensions may explain some of the differences in risk observed in different branches of the industry with similar fibre counts. In the absence of information on the distribution of fibre sizes, fibre counts based solely on optical microscopy constitute an inadequate basis for extrapolating from (say) a textile factory to other situations.

Other sources of error in predicting risk may include failure to take account of the reduction in the relative risk of lung cancer after exposure ceases, the variation in regulated fibre counts resulting from the use of the eyepiece graticule, the change from static to personal sampling, and an inadequate allowance for the effect of the use of some crocidolite at Rochdale.

Control limit for chrysotile

A central estimate of the life-long risk caused by 20 to 30 years' exposure in chrysotile textile manufacture of 0.5 f.ml^{-1} and an assumed average exposure to 0.25 f.ml^{-1}. This corresponds to a loss of expected life of about one month average over the whole workforce, but of about 12 years for affected individuals. There are several reasons for thinking that this estimate is too high, while the observations on men first employed at Rochdale since 1950 suggest that it may be too low.

A standard limit defined only by number of regulated fibres must be expected to control risks to different extents in situations in which the configurations of the fibre are not the same.

Within industry, the most hazardous occupation is insulation work for which measures of intensity of exposure are lacking and which often gives rise to exposure to amphiboles. Friction product workers, by contrast, appear to have lower risks than textile workers if exposed to the same numerical count of fibres. The position with regard to asbestos cement workers, using only chrysotile, is uncertain.

Asbestos in buildings

Estimation of the effect of environmental exposure in buildings is further complicated by: (a) the need for extrapolation to very low levels; and (b) the unreliability of most measures of exposure. At the very low levels encountered only measurements made by transmission electron microscopy have any validity. These can then be related to counts made with the optical microscope from experience in the textile industry.

The review of published studies by the Ontario Royal Commission (1984) and measurements made in British buildings on behalf of the Department of the Environment suggest that exposure to true asbestos fibres of regulated sizes within asbestos-containing buildings is seldom more than 0.0005 f.ml^{-1} above background (as seen by optical microscopy). Exposure to this level for a working week in an office for 20 years in adult life or for 10 years or so at school, or to lower average levels for more prolonged times at home is calculated to produce a life-time risk of death of one in 100 000. If 20% of the population experience such exposure, this would imply that one death a year was caused by it in the whole country. This assumes that the exposure is to chrysotile. Exposure to crocidolite (and possibly also to amosite) must be expected to produce effects that are appreciably greater.

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Appendix

Amended version of table in previous report to the Health and Safety Commission

The Table, which has been included at the request of Professor E D Acheson and Dr M J Gardner, is an amended version of Table 3 in their report to the Health and Safety Commission (Acheson and Gardner, 1983) and should replace it.

Reference

Acheson E D, Gardner M J (1983) *Asbestos: The Control Limit for Asbestos* Health and Safety Commission HMSO, London

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Table 3 Mesotheliomas by sex, fibre type and site in cohort studies of asbestos-exposed workers[1]

Sex	Type of exposure	Reference	Number in cohort	Number of deaths	Lung cancer deaths: observed	Lung cancer deaths: excess[2]	No of mesotheliomas: pleural	No of mesotheliomas: peritoneal	No of mesotheliomas: total	Mesotheliomas: % of all deaths	Mesotheliomas: Ratio to excess lung cancer deaths
Men	*Mining and milling*										
	Chrysotile	McDonald *et al* (1980b)[3]	9,820	3,291	220	46.0	10	0	10	0.3	0.2
		Nicholson *et al* (1979)	544	178	28	17.0	1	0	1	0.6	0.1
		Rubino *et al* (1979)	933	332	11	0.6	0	0	0[4]	0	0
	Anthophyllite	Mountin *et al* (1974)[5]	1,841	348	21	0.4	0	0	0	0	0
	Talc	Kleinfeld *et al* (1967b)	220	91	9	5.8	1	1	2	2.2	0.3
		Brown *et al* (1979)	382	74	9	5.7	?	?	1	1.4	0.2
	Crocidolite	Hobbs *et al* (1980)	4,960	526	59	28.8	17	0	17[6]	3.2	0.8
Men	*Manufacture*										
	Chrysotile	Thomas *et al* (1982)	1,540	351	28	-5.8	2	0	2	0.6	—
		Weiss (1977)	264	66	4	-0.3	0	0	0	0	—
		Dement *et al* (1982)	746	191	26	18.5	0	1	1	0.5	0.1
		McDonald *et al* (unpub a)	2,543	570[7]	59[8]	29.4[9]	0	1	1	0.2	0.0
		McDonald & Fry (1982)	3,890	1,508	?	?	0	0	0	0	—
	Crocidolite	McDonald & McDonald (1978)	93	43	8	4.0[10]	X	X	9[11]	18.6	2.0
	Amosite	Seidman *et al* (1979)	828	528	83	39.9	7	7	14	2.7	0.2
		Acheson *et al* (1981)	4,882	431[12]	57[8]	27.9[9]	4	1	5	1.2	0.2
	Mixed	Newhouse & Berry (1979)[7]	2,587	565	103	59.8	19	27	46	8.4	0.8
		Newhouse *et al* (1982)[7]	8,804	1,339	143	3.5	8	0	8	0.6	2.3
		Peto *et al* (1977)	822	293	48	26.1	9	0	9	3.1	0.3
		Henderson & Enterline (1979)	1,875	781	63	39.7	?	?	4	0.5	0.1
		Robinson *et al* (1979)	2,666	912	49	12.9	4	5	13[6]	1.4	1.0
		Hughes & Weill (1980)	5,845	601	51	1.9	0	0	0[13]	0	0
		Mancuso & Coulter (1963)	1,266	175	15	9.6	0	4	4	2.3	0.4
		McDonald *et al* (unpub b)	4,137	889[7]	57[8]	2.5[9]	10	4	14	1.6	5.6
Men	*Insulation*										
	Mixed	Kleinfeld *et al* (1967a)	152	46	10	8.6	1	2	3	6.5	0.3
		Selikoff *et al* (1979)	632	478	93	79.7	11	27	38	7.9	0.5
		Selikoff *et al* (1979)	17,800	2,271	429	323.4	63	112	175	7.7	0.5
		Elmes & Simpson (1977)[7]	162	122	35	30.0	8	5	13	10.7	0.4
		Newhouse & Berry (1979)[7]	1,368	83	21	15.4	4	6	10	12.0	0.6
Men	*Shipyards*										
	Mixed	Rossiter *et al* (1980)	6,076	1,043	84	-16.3	29	2	31	3.0	—
		Kolonel *et al* (1980)	4,779	383	35	2.5	0	0	0[14]	0.8	0
Women	*Manufacture*										
	Chrysotile	McDonald & Fry (1982)	848	122	1	-1.5	0	0	0	0	—
		Acheson *et al* (1982)	370	177	6	1.2	1	0	1	0.6	0.8
	Crocidolite	Jones *et al* (1980)	378	166	12	8.2	13	4	17[6]	10.2	2.1
		McDonald & McDonald (1978)	83	13	0	-0.6[10]	X	X	2[11]	15.4	—
		Acheson *et al* (1982)	757	219	13	6.8	3	2	5	2.3	0.7
	Mixed	Peto *et al* (1977)	284	24	2	1.1	1	0	1	4.2	0.9
		Newhouse & Berry (1979)[7]	922	200	27	23.8	13	8	21	10.5	0.9
		Newhouse *et al* (1982)[7]	4,219	299	6	-5.3	2	0	2	0.7	—
		Robinson *et al* (1979)	544	128	14	12.3	1	1	4[6]	3.1	0.3
		Mancuso & Coulter (1963)	229	20	4	3.8	0	1	1	5.0	0.3

[1] Based on Table 2, McDonald and McDonald (1981)
[2] Excess of observed over expected deaths
[3] One possible case (Rubino *et al*, 1979); 2 cases not meeting criteria (Hughes and Weill, 1980)
[4] Three cases after end of follow up
[5] Updated 1983; 60 pleural and 4 peritoneal, personal communication
[6] Site unknown for 4 mesotheliomas in men and 2 in women
[7] Updated 1983: 34 pleural and 5 peritoneal, personal communication
[8] Deaths 20 years after first employment only
X Of the 10 mesotheliomas in both sexes 8 were peritoneal and 2 were peritoneal and pleural

[9] Deaths 20+ years after first employment
[10] Includes women
[11] deaths 10+ years after first employment
[12] 11 lung cancer deaths were possibly pleural mesotheliomas
[13] From: Acheson E D, Gardner M J, Winter P D and Bennett C. Cancer in a factory using amosite asbestos *International Journal of Epidemiology* 13, 3–10

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