Asbestos

The control limit for asbestos

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An up-date of the relevant sections of *The Ill-effects of Asbestos upon Health* prepared by the authors for the Advisory Committee on Asbestos and published in *Asbestos: vol 2: final report of the Advisory Committee* Health and Safety Commission 1979 HMSO

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Contents

Introduction

1 Our brief is to prepare a paper for the Health and Safety Commission which will examine in relation to the control limit for asbestos:

> "1. Any material which has been suggested was available but not presented to the earlier Advisory Committee on Asbestos which would have influenced significantly your joint report to the Committee.
>
> 2. Any published data since the time of the report that would cause you to think that significant change should now be made to the report as then published."*

2 The review is to be limited to the issue of *the control limit in the workplace* and the evidence bearing upon it, including the question of the desirability of different limits for different types of fibre. We have not been required to bring up-to-date the sections of our report which dealt with asbestos outside the workplace—for example, inside schools and public buildings, out of doors, and in drinking water.

3 In the main part of this review we will discuss the relevant scientific literature published since 1979 in relation to each of the main conclusions of our previous report which are within our present terms of reference. To assist the reader a résumé of each of these conclusions (in italics) will precede the discussion of the recent literature, the reference to the appropriate paragraphs in the 1979 report being given in parentheses.

4 A review of an unpublished paper by Dr J G Morris dated 24 February 1978 which was circulated to the Medical Working Group of the Advisory Committee on Asbestos in April of that year is given in Appendix A. Appendix B consists of a critique by Dr J Steel of the dust measurements in the paper by Dr J M Dement and colleagues describing the mortality of South Carolina textile workers exposed to chrysotile. Appendix C contains some detailed comments by Professor M Turner-Warwick on the applicability to asbestos-related diseases of the indices of adverse effects used in the morbidity survey by the British Occupational Hygiene Society (1983). Appendix D includes a summary of some of the main problems in the interpretation of the available data on dust measurements and their relationship to the occurrence of disease.

5 We have also examined various other papers provided for us by the Health and Safety Executive. These include excerpts of a transcript of a television programme broadcast by Yorkshire TV on 20 July 1982; a list of points which arose out of the programme or out of research for it which were the subject of a meeting held by the Health and Safety Executive on 26 August 1982; papers and correspondence dealing with various cases of mesothelioma; a reprint of a paper by Drs V L Henderson and P E Enterline on mortality in a US asbestos factory; a draft of a study on *The health experience of two UK asbestos factories* by a sub-committee of the British Occupational Hygiene Society prepared for a meeting in 1980; some material concerning six fatal cases of lung cancer in persons who had entered the asbestos industry subsequent to 1951; and some material relating to the cohort of workers studied by Dr J G Morris (see Appendix A).

6 We summarise the points contained in this material which are relevant to our terms of reference as follows:

(a) The incidence of pleural mesothelioma, its relationship to fibre type and the bearing this has on mesothelioma at Rochdale.
This is discussed in the context of the recent scientific literature in paras 24 to 40, and with particular reference to Rochdale in para 30. The evidence that crocidolite has been a factor in the occurrence of the cases of pleural mesothelioma at Rochdale has strengthened since our last report.

(b) The prevalence of "adverse effects" and their relationship to asbestos in persons employed in Rochdale since 1951.
This is discussed in paras 59 to 64, para 95, and in Appendix A and Appendix C.

(c) The mortality from lung cancer at Rochdale in persons first employed since 1951.
The mortality from lung cancer is dealt with in relation to the recent literature in paras 65 to 80 and 89 to 103 and in respect to Rochdale in para 75. The finding of a higher mortality in men first exposed after 1950 than previously (Peto, 1980a) now seems to have been an anomaly due to small numbers (Peto J, personal communication).

7 Henderson and Enterline (1979) report a large number of mesotheliomas amongst the younger workforce of a factory from which they had previously studied a group of pensioners (Enterline and Henderson, 1973), only one of whom was known to have developed a mesothelioma. The occurrence of a large number of mesotheliomas in younger men in this workforce had previously been noted by Borow *et al* (1973), and was reported in our previous review (Acheson and Gardner, 1979a, p 29). Crocidolite is known to have been used in this factory, but nothing was or is known about the history of fibre exposure in these mesothelioma cases. The recent paper by Henderson and Enterline does not contain any new information with a bearing on the control limit for chrysotile, unless one takes the view that crocidolite was not a factor in the causation of these cases.

* Excerpt from letter from Dr K P Duncan to Professor E D Acheson dated 15 November 1982.

Trends in asbestos imports

8 *For practical purposes the types of asbestos fibre important in the UK were shown to be chrysotile, crocidolite and amosite. In 1975 chrysotile accounted for about 85% of the total imports of fibre, with almost the whole of the remainder being amosite. The considerable expansion in imports of amosite since the end of World War II was noted, so that in spite of the discontinuation of crocidolite imports in 1970, the absolute and proportional amount of amphibole fibre (in the form of amosite) imported in 1975 was considerably greater than that in 1945 (paras 72, 74 and 75).*

Up-date

9 Table 1 brings up-to-date the information on imports of raw asbestos fibre into the UK published in our previous report (Acheson and Gardner, 1979a). The Table includes figures for the serpentine asbestos, chrysotile (white asbestos), and for the amphiboles, crocidolite (blue asbestos) and amosite (brown asbestos). The most striking change is that the import of amosite has virtually ceased, as shown in Figure 1 (the estimate for 1982 is 16 tonnes). Of the 2700 tonnes of amosite imported during 1978, the large majority (2000 tonnes) was incorporated into insulation board, with almost all the remaining 700 tonnes being used for asbestos cement pressure pipes. In 1980 and 1981 all the imported amosite was used in the latter application. The manufacture of insulation board is now carried out with other materials. Chrysotile imports have also declined, but at 76 400 tonnes in 1981 are estimated still to be about 50% above the 1946 figure. The largest uses of chrysotile during 1981 were in asbestos cement (28 050 tonnes), friction materials (11 200 tonnes) and floor tiles (8000 tonnes), with a variety of other applications (including 3000 tonnes in textile products) making up the remaining 29 150 tonnes (Table 2).

10 Although imports of amphiboles as raw fibre into the UK have at present effectively ceased we note that the import of manufactured products containing amphiboles continues. Also, substantial quantities of these materials remain in the insulation of buildings, ships and railway carriages, and in certain cement products, including pressure piping. Overall, more than half-a-million tonnes of amphiboles had been imported into the UK up to 1982. From 1 January 1983 the utilisation, repair or demolition of materials containing amphiboles are subject to control limits of 0.5 fibres/ml for amosite and 0.2 fibres/ml for crocidolite.

11 As far as production is concerned, chrysotile is now for practical purposes the only type of asbestos used in manufacture in the UK. However it will be necessary for many years to come to continue to control the servicing and demolition of previously produced articles containing amphiboles.

The asbestos-related diseases

12 *ASBESTOSIS, which may be defined 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) pleura, LUNG CANCER, and MESOTHELIOMA of the PLEURA or PERITONEUM were considered as having been universally accepted as diseases with a causal relationship to the inhalation (and for peritoneal mesothelioma possibly the ingestion) of asbestos fibre.**

13 *With regard to other putative asbestos-related diseases we concluded that there is a risk (small in absolute terms) of CANCER OF THE LARYNX associated with mixtures of asbestos containing amphiboles. In respect of CANCERS OF THE ALIMENTARY TRACT we again noted an association with amphibole, that the clinical and pathological data available about such cancers were often sketchy and that some at least were likely to have been undisclosed cases of peritoneal mesothelioma. However, some of the excesses noted in men exposed to amphiboles were so large that an association between cancers of the alimentary tract and inhalation or ingestion of such fibres seemed likely (paras 8—12).*

* *Benign pleural effusion* and *pleural thickening*, noted as asbestos-related in our previous report, are not considered further here.

Up-date

14 In recent publications up-dating the mortality experience of 17 800 North American insulators and workers in a New Jersey amosite asbestos factory, Selikoff has continued to observe excesses of deaths from cancer of the oesophagus, stomach, large bowel, mouth and pharynx and kidney (Selikoff *et al*, 1979; Seidman *et al*, 1979) but has shown that an apparent excess of deaths ascribed to cancer of the pancreas in the insulators was likely to be due to mis-diagnosed peritoneal mesotheliomas and cancers of other parts of the alimentary tract (Selikoff and Seidman, 1981). The men in each of these studies also show remarkably high cancer rates for all other cancers combined, and this is true whether the original death certificate diagnosis is accepted or a 'corrected' diagnosis based on examination of hospital records is used. The latest

published paper on the Barking asbestos factory shows an excess of gastro-intestinal cancers (60 observed deaths; 44 expected) (Newhouse and Berry, 1979), as also does the most recent report on production and maintenance employees in the United States (55 observed; 40 expected) (Henderson and Enterline, 1979). No significant excess of deaths from alimentary tract cancer was reported in a study of London insulation board makers exposed to amosite under dusty conditions, but only 7% of the cohort have died and the likelihood of having detected a 3:1 relative risk such as was observed by Selikoff is small (Acheson *et al*, in press). The most recent report on mortality among men at Rochdale exposed principally to chrysotile, but also to crocidolite, supported the earlier finding of no excess deaths from alimentary tract cancer as a whole (14 deaths observed; 12.6 expected) (Peto, 1980a).

15 McDonald and her colleagues have recently reported a slight excess of deaths from alimentary tract cancer (26 observed; 17.1 expected) in a South Carolina textile factory (McDonald *et al*, unpublished a). This study is important because chrysotile was the only fibre used (see also para 77). No excess of alimentary tract cancer (132 deaths observed; 134.6 expected) was found in an English factory manufacturing friction materials from chrysotile (Berry and Newhouse, 1983). Likewise no excesses were reported from four asbestos cement factories—two in New Orleans using chrysotile (predominantly) and crocidolite (25 deaths observed; 50.1 expected) (Weill *et al*, 1980), one in South Wales in which the fibre used was almost exclusively chrysotile (18 observed; 19.6 expected) (Thomas *et al*, 1982), and the fourth in Denmark using chrysotile, crocidolite and amosite (31 observed; 29.9 expected), although in this study there was a slight suggestion of an excess of stomach cancer (Clemmesen and Hjalgrim-Jensen, 1981)*. No excess mortality from alimentary tract cancer has been observed in a cohort of 6200 West Australian ex-crocidolite miners who suffered heavy dust exposure (Hobbs *et al*, 1980), or in two groups of women engaged in the manufacture of gas masks in World War II (Wignall and Fox, 1982; Acheson *et al*, 1982).

16 It can be seen that the evidence published since our previous report has tended to weaken the view that exposure to asbestos causes alimentary tract cancer. Large excesses 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 to asbestos fibre *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 populations with which they have been compared need to be taken into account.

17 Two recent studies of women involved in the manufacture of gas masks from crocidolite in World War II have reported a significantly increased mortality from ovarian cancer (Wignall and Fox, 1982; Acheson *et al*, 1982). These findings supplement an earlier report of excess ovarian tumours among the most severely exposed group of female asbestos factory workers manufacturing products containing amphiboles and chrysotile (Newhouse and Berry, 1979). A group of women who manufactured civilian gas masks out of chrysotile experienced no such increase in mortality (Acheson *et al*, 1982), nor was any excess found among a group of women involved in the manufacture of friction materials (Newhouse *et al*, 1982). It is not yet clear whether the excess mortality ascribed to this cause is in fact due to ovarian tumours or to misdiagnosed peritoneal mesotheliomas.

18 Three further case-control studies of laryngeal cancer have been published since our last report. A Canadian study supports the role of asbestos in cancer of the larynx, although the influence of this factor is small compared with tobacco and alcohol (Burch *et al*, 1981). A study by Newhouse *et al* (1980) is negative. It should be pointed out, however, that the latter study had a 30% chance of missing a relative risk of 2 associated with asbestos exposure and that the upper 95% confidence limit for the relative risk of laryngeal cancer is 2.1. An excess of cancer of the larynx has been reported in a cohort study of asbestos cement workers in Denmark (6 observed; 2.9 expected), where exposure was to chrysotile, crocidolite and amosite (Clemmesen and Hjalgrim-Jensen, 1981).

19 Ross and colleagues (1982) have suggested that there may be an association between non-Hodgkin's lymphoma of the alimentary tract and exposure to asbestos. A subsequent report of a case-control study of non-Hodgkin's lymphoma estimated a relative risk of 1.3 (but with wide confidence limits of 0.5 and 3.1) due to asbestos after adjusting for other relevant exposures (Bengtsson *et al*, 1982). The debate on this matter continues (Olsson and Brandt, 1983).

*Our attention has been drawn to a study of an asbestos cement factory in Belgium in which an excess of alimentary but not of respiratory cancer was detected (Lacquet *et al*, 1980). This study appears to have serious methodological shortcomings.

The relationship of health effects to fibre type

20 *In animals, experimental work involving inhalation and pleural implantation shows that chrysotile can produce at least as many mesotheliomas and malignant lung tumours as samples of amphiboles.*

21 *For mesothelioma in man, evidence from miners, from process workers exposed to a single fibre type, from the distribution of neighbourhood and domestic cases, and from the geography of mesothelioma pre-*

sents a powerful case from four different points of view that crocidolite has been more dangerous than chrysotile. The position of amosite may be intermediate between crocidolite and chrysotile. It can be concluded that exposure to chrysotile alone so far has rarely been shown to cause mesothelioma. Evidence in man relating lung cancer and asbestosis to fibre type is inconclusive, but the small amount which exists is consistent with the view that exposure to amphiboles or mixtures rich in them have been more dangerous than to chrysotile alone (paras 111—164).

Up-date

Animal experiments

22 A number of recent papers and reviews relating to experimental work in animals have upheld the hypothesis of Stanton that durable fibres, of which asbestos is but one example, can cause cancer irrespective of their physicochemical nature, provided that their configuration falls within well-defined ranges of diameter and length with thin long fibres being most carcinogenic (Harington, 1981; Stanton *et al*, 1981; Craighead and Mossman, 1982). It has been suggested, however, by Bertrand and Pezerat (1980) that there may be no limit of length or diameter below which carcinogenicity disappears but that carcinogenicity may be a continuous increasing function of the aspect ratio of the fibres. Up to 14 fibrous materials are now known to produce malignant neoplasms following implantation in the pleural or peritoneal cavities of animals: amosite, anthophyllite, chrysotile, crocidolite, and tremolite; borosilicate glass, aluminium silicate, glass, mineral wool, aluminium oxide, potassium titanate, silicon carbide and sodium aluminium carbonate; wollastonite and attapulgite (Harington, 1981; Stanton *et al*, 1981).

23 As far as the animal work is concerned, therefore, there is little change in the position we summarised in 1979: namely that in the experimental situation specially prepared samples of chrysotile are at least as carcinogenic as are amphiboles both in implantation and inhalation experiments. Davis has suggested that the carcinogenicity of chrysotile may be increased due to the separation of large fibres into individual fibrils in the tissues (Davis, 1982).

Mesothelioma in man

24 Peto and co-workers have drawn attention to the relationship between the incidence rates of both peritoneal and pleural mesothelioma and the third power (approximately) of the interval since first exposure to asbestos (Peto *et al*, 1982). They have calculated that the highest relative risks of *peritoneal mesothelioma* so far reported are in North American insulators, workers in a New Jersey amosite factory, and workers at Barking, all of whom were exposed to amphiboles. Peritoneal mesotheliomas have also been reported from Canada and Nottingham among gas-mask makers exposed to crocidolite (McDonald and McDonald, 1978; Jones *et al*, 1980; Wignall and Fox, 1982), and recently from Western Australian crocidolite miners (Hobbs, 1983). In the last two studies mentioned, however, the numbers of cases have been very small compared with the numbers of cases of pleural mesothelioma (Nottingham: 5 peritoneal, 34 pleural; Western Australia: 4 peritoneal, 60 pleural). Of five mesotheliomas reported as the underlying cause of death from a British factory using almost exclusively commercial amosite in the manufacture of insulation board, one was a peritoneal tumour (Acheson *et al*, 1981). No peritoneal mesotheliomas have been reported from Quebec among chrysotile miners and millers who were not elsewhere exposed to crocidolite (McDonald, 1980), or from some factories manufacturing friction materials or asbestos cement from chrysotile. A single peritoneal mesothelioma has been reported from a textile factory in South Carolina using exclusively chrysotile (Dement *et al*, 1982; McDonald *et al*, unpublished a). With this exception all reported cases of peritoneal mesothelioma seem likely to have been exposed to one or both of the amphiboles, amosite or crocidolite. Difficulties in diagnosis and other factors, as yet unknown, may explain the variation in estimated life risks of peritoneal mesothelioma amongst those exposed to amphiboles. These range from zero at Rochdale to a figure perhaps as high as 10% for American insulation workers and factory workers first exposed to amosite at age 20 (Peto *et al*, 1982).

25 A study of 144 cases of mesothelioma known by Cape Industries to have occurred in their employees has recently been published (Browne and Smither, 1983). It is not certain what proportion of the total number of cases that have occurred in workers and ex-workers these cases represent, and little numerical information is given about the populations from which the cases were derived. Within these limits the results support a relationship between both pleural and peritoneal mesothelioma and exposure to amphiboles, particularly crocidolite. The evidence suggests that workers who developed peritoneal mesothelioma may have been exposed to heavier doses of fibre than those who developed pleural mesothelioma.

26 Table 3 shows the excess lung cancer deaths over those expected and the numbers of deaths due to pleural and peritoneal mesothelioma for miners and millers, industrial process, insulation and shipyard workers by fibre type. A substantial difference also exists in the incidence of pleural mesothelioma between workers exposed to chrysotile alone and those who have been exposed to amphiboles, although the differences are not as great as those for peritoneal mesothelioma which have been described above. In men, 0.3% of the deaths amongst chrysotile miners (McDonald *et al*, 1980b) were due to pleural mesothelioma as opposed to 8.8% among crocidolite miners (Hobbs *et al*, 1980). Forty-four additional deaths from pleural mesothelioma have recently been

reported among the West Australian crocidolite miners but these cannot be included in the Table as the up-dated total number of deaths is not known. In the remainder of the Table (manufacture, insulation, shipyards) only two (0.1%) deaths (out of 2752) from pleural mesothelioma occurred among men exposed to chrysotile only (excluding Dement *et al* (1982) which is a sub-cohort of McDonald *et al* (unpublished a)) but 181 (1.7%) of the 10447 deaths which occurred in association with exposures to amphiboles alone or with chrysotile were pleural mesotheliomas. Among women all but one of 34 deaths from pleural mesothelioma (3.0% of the total of 1103) were associated with amphiboles or mixed exposures. It has previously been suggested that the mortality from mesothelioma in a workforce may be used to predict other asbestos related cancer mortality (McDonald and McDonald, 1981). However, as can be seen from Table 3, the ratio between the numbers of mesothelioma deaths and excess lung cancer mortality varies between wide limits.

27 Talent and his co-workers have undertaken a survey of a list of black ex-employees of the Cape crocidolite mines in South Africa, which is not included in Table 2 because it measures the prevalence rather than mortality due to pleural mesothelioma (Talent *et al*, 1980). However, it supports a high risk of this disease associated with crocidolite. The follow-up was limited to 1185 men who were citizens of Bophuthatswana, most of whom had worked in the mines for less than five years, and who had been recruited into employment in the mines at least 11 years before the survey. Two hundred and fifteen of the men were found to have died prior to the survey, but nothing could be discovered of the causes of death. Of 755 ex-employees who were located four were found on clinical examination and biopsy to be suffering from pleural mesothelioma (a prevalence rate of 0.5%). Two further cases of pleural mesothelioma were discovered shortly after the completion of the survey. Given an average duration of illness of about two years a prevalence of 0.5% suggests an annual incidence at the time of the survey of about 1 in 400. The prevalence of mesothelioma was found to increase with increasing time since first exposure – from 0.4% at 16—20 years, to 1.3% at 21—25 years, and 2.5% beyond 25 years. In further studies of 947 ex-employees of these mines not on the list, 11 other cases of pleural mesotheliomas were identified (a prevalence of 1.2%). Some of the men in the last group may have attended for examination because they were ill.

28 Rossiter and Coles (1980) found 31 mesotheliomas among 1043 deaths in a cohort of 6076 British naval dockyard workers who had been exposed to amphiboles and chrysotile. There was a deficiency (84 observed; 100 expected) of deaths from lung cancer in this group of men. This is an unexpected deficit. The reason for it is unknown but it has been suggested that it may be related to lower cigarette smoking habits in these workers or possibly to exposure to asbestos fibres of an unusual composition in terms of size due to the use of respiratory protection equipment by the men.

29 The lack of pleural mesotheliomas among 872 deaths in the workforce of a factory manufacturing textiles from chrysotile in South Carolina, in which the men suffered a substantial excess mortality from lung cancer, is of particular interest (McDonald and Fry, 1982). In the same paper, McDonald and Fry also report an absence of mesotheliomas among 1630 deaths in a factory using only chrysotile in the manufacture of friction materials. The authors contrast these findings with the experience of another American factory which used amphiboles as well as chrysotile where 14 deaths from mesothelioma occurred among 895 deaths (McDonald *et al*, unpublished b).

30 Peto has suggested that the rate of mortality from pleural mesothelioma at Rochdale, where the principal fibre used was chrysotile, is similar to that at Barking where in addition to chrysotile large quantities of amphiboles were also used (Peto, 1980b). His comparison was between three sub-cohorts from Rochdale, selected because they had at least 10 (and in one case more than 20) years' exposure, and the complete Barking cohort (excluding only laggers), which had large numbers of men and women exposed for less than two years. Since the incidence of pleural mesothelioma depends on duration of exposure, these figures could be interpreted to indicate a higher risk, for any given length of employment, at Barking than at Rochdale, rather than similar risks. Peto's implied conclusion was that the heavier crocidolite exposure of workers at Barking more than compensated for their shorter duration of exposure. Subsequently a study of lung tissue in 12 cases of mesothelioma and 12 controls, all of whom were men who had worked at Rochdale, has shown a substantial burden of crocidolite as well as chrysotile (Wagner *et al*, 1982). According to the authors the lung tissue of eight of the cases of mesothelioma reported by Peto and colleagues (1977) are included in this series. As no differences in the nature of the fibre burdens were found between the mesothelioma cases and controls, it is difficult to attribute the tumours with certainty to either fibre type. The controls contained at least five deaths from asbestos-related causes, four from lung cancer and one from asbestosis. The crocidolite fibre counts in both cases and controls are similar to those found in the lungs of gas-mask workers by Morgan and Holmes (1982). The results of this study, therefore, suggest that substantial amounts of crocidolite must have been used at the Rochdale factory.*

* This is borne out by recent data which suggest that about 10000 tonnes of crocidolite fibre and yarn were used between 1931—1970 (Doll R, personal communication), not "at least 2,500 tonnes" as we indicated on p 26 of our previous report (Acheson and Gardner, 1979a).

31 Newhouse, Berry and Skidmore (1982) have carried out detailed studies of a factory which has manufactured friction materials from chrysotile since 1920, but which utilised crocidolite in a particular area of the factory (Skidmore and Dufficy, 1983) for two periods from 1929 to 1933 and from 1939 to 1944 respectively. A total of 13 460 subjects who have been employed since proper records were set up in 1941, and of whom over 99% were traced to the end of 1979, were included. Among these persons 10 deaths due to pleural mesothelioma were found. In order to study the relevant environmental factors involved four controls for each case were selected, matched for sex, year of starting work, year of birth, and survival up to the time of death of the case of mesothelioma. In addition each control had to have been employed at the factory during one or more of the periods when crocidolite was used for the same time as the case. The results indicate that eight of the ten mesothelioma cases had definite and one had fringe exposure to crocidolite, as compared with three definite and seven fringe exposures to crocidolite among the 40 controls (Table 4a). A strong and significant association was thus demonstrated with crocidolite exposure. An association with exposure to chrysotile of at least 5 fibres/ml was also demonstrated (Table 4b), but combined exposure to chrysotile and crocidolite may also be relevant (Table 4c). In an attempt to hold constant the effect of chrysotile, those matched sets where the case and at least one of the controls had been exposed to 5 fibres/ml of chrysotile were examined. Within these sets it was possible to show an association with exposure to crocidolite (five out of six such cases and two out of ten such controls had been exposed to crocidolite; a two-sided significance test gives $p = 0.06$). A reverse analysis, in matched sets where the case and at least one control had definite exposure to crocidolite, is limited by small numbers, with all three such cases and two out of three such controls being exposed to at least 5 fibres/ml of chrysotile. Three further pleural mesotheliomas are known to have occurred at the factory, but adequate reasons for their exclusion are given. They were not included in the study population as they had, in fact, left before the filing system was set up in 1941. A further mesothelioma death, which occurred in late 1980, of a man who had worked at the factory for only two weeks, is reported in a more recent paper (Berry and Newhouse, 1983). There is no evidence that this man was exposed to crocidolite in the factory. Examination of lung tissue from seven of the mesothelioma cases showed crocidolite and chrysotile in excess of 1×10^6 fibres per gram. Unfortunately, no samples of lung tissue from controls were examined.

32 The results of the case/control study are compatible with both crocidolite and chrysotile exerting an influence, possibly jointly (Table 4c), on the incidence of mesothelioma. However, an analysis (Berry G, personal communication) to investigate this, taking account of the matching and disregarding fringe exposure to crocidolite, finds no evidence of any synergistic effect due to the mixture on top of the additive effects of crocidolite and chrysotile. Acheson and Gardner (1979b) suggested the possibility of a synergistic interaction between chrysotile and amphiboles on the incidence of mesothelioma on the basis of studies of the quantities of fibres of different types in lung tissue and epidemiological data, but this was not borne out in later data (Acheson and Gardner, 1980a).

33 Langer and McCaughey (1982) have described a case of pleural mesothelioma in a man whose sole reported exposure to asbestos was to chrysotile during brake maintenance and repair. Fibrils of chrysotile but not of amphiboles were found in the thoracic tissues at autopsy.

34 McDonald and McDonald (1980) attempted to ascertain all fatal malignant mesotheliomas in Canada (1960—75) and the US (1972), and obtained records of 668 cases. A control matched for sex, age and year of death in which pulmonary secondaries from a non-pulmonary tumour were present was selected for each case. Occupational histories were obtained from cases and controls. By far the highest relative risk (46.0) was for insulation work, with asbestos production and manufacture (6.1) second, and heating trades other than insulation (4.4) third. Although this survey included all mesotheliomas that could be found in Canada during a 16-year period (1960—75), only seven of the subjects had been associated with the Quebec chrysotile mines, four having been employed in the mines and three being children of employees. No other subjects with mesothelioma who had lived in the Quebec mining area were found. This study supports the reports which we summarised previously which showed the very low incidence of mesothelioma in and about the Quebec chrysotile mines, although these have been established on a large scale since early in the century (Acheson and Gardner, 1979a). Although pleural and peritoneal mesotheliomas were considered together in this survey, a particularly strong relationship was noted between work in insulation and the occurrence of peritoneal mesothelioma.

35 In a study of the geographical distribution of deaths from pleural mesothelioma during 1968—78 in England and Wales, cases were concentrated in areas where asbestos, in particular amphiboles, was used in the relevant past (Gardner *et al*, 1982; Gardner, 1983a). Among men the major locations were naval dockyards and ports where shipbuilding and repairing were carried out, whereas among women a high occurrence of mesothelioma was found in areas where gas masks had been manufactured. For both sexes there were areas with high rates on the eastern side of London, and in Leeds and Rochdale. These findings are consistent with the view that in this country a large proportion of mesothelioma deaths are asbestos-related.

36 Acheson and his colleagues compared the mortality over a period of 40 years of two groups of Lancashire women who had manufactured respectively service gas masks (containing crocidolite) at Leyland and civilian gas masks (containing chrysotile) at Blackburn (Acheson *et al*, 1982). Mesothelioma was mentioned on five of the 219 death certificates from the former (three pleural, two peritoneal) and one (pleural) of 177 from the latter. The woman who died from pleural mesothelioma in the civilian gas-mask factory at Blackburn had also worked in another gas-mask factory in the same city where crocidolite was used. The mesothelioma cases from Blackburn referred to in the paper of Morgan and Holmes (1982) also worked in the latter factory (Grimes P, personal communication).

37 If it is accepted that, from the point of view of the risk of mesothelioma, crocidolite and amosite are more dangerous than chrysotile it does not necessarily follow that a fibre of a particular configuration of one mineral is more dangerous than that of another. Walton (1982) has pointed out that crocidolite produces fine straight fibres more easily (i.e., with the application of less energy) than chrysotile, and that in the past people working with crocidolite have been exposed to substantially higher concentrations of fibres in "the carcinogenic size range" than those working with other varieties. He further points out that most of these fibres would not be visible by optical microscopy and would therefore not be counted in routine industrial hygiene measurements.

Examination of human lung tissues

38 Studies of blocks of lung tissue were carried out in 99 cases and matched controls from the North American survey of mesothelioma described above (McDonald *et al*, 1982). Electron microscopy revealed equal quantities of chrysotile among the male cases and their controls. However, there were more cases than controls (26 cases compared to eight controls) with more than 1×10^6 fibres of amosite per gram, and more cases than controls (15 cases compared to five controls) with more than 1×10^6 fibres of crocidolite per gram. In the females there were slight excesses of chrysotile and amphiboles among the cases compared to the controls. Although these findings are consistent with the view that the male mesothelioma cases inhaled more amphiboles than the controls, the fibre burden of lung tissue at autopsy does not necessarily reflect the nature of the fibres which penetrate to the pleura. Sebastien and his colleagues (1982) have shown that chrysotile may be present in the pleura in quantities unrelated to the amount and type of asbestos in the lung. Pooley and Clark (1979) have shown that the configuration of fibres of the three common types of asbestos recovered from human lung tissue differs widely, and that the shortest fibres with the smallest diameter distribution on average are chrysotile. The biological significance of these fibres is uncertain (Walton, 1982).

39 Wagner, Pooley and their colleagues (1982) compared the lung burden at autopsy of cases submitted to the British Pneumoconiosis Medical Panel with control autopsies and mesotheliomas from various sources. Greater quantities (by a factor of about 100) of both crocidolite and amosite were found in the Panel cases than in the controls, but the quantities of chrysotile were similar. The amount of amphiboles was similar in each category of Panel cases, namely mesothelioma, lung cancer and asbestosis, but in the cases of asbestosis the amount of amphiboles, but not of chrysotile, related well quantitatively to the severity of the disease. Morgan and Holmes (1982) measured the concentrations of amphiboles fibres in the lungs of 26 mesothelioma deaths among women who made gas masks in three English cities. In 19 cases levels of greater than 1×10^6 fibres per gram of dried lung were found, but there were no controls.

Amosite and mesothelioma

40 The occurrence of four deaths attributed to pleural mesothelioma and one to peritoneal mesothelioma among 431 deaths in London insulators exposed to amosite has already been noted (Acheson *et al*, 1981). These results, the analysis of American insulators reported by Peto and his colleagues (Peto *et al*, 1982) and referred to in para 24, and the findings of the analysis of the fibre burden in the lungs of American and Canadian cases of mesothelioma support our previously expressed view that the risk of mesothelioma in association with amosite is greater than with chrysotile. However the nature of the lung fibre burden of the London insulators has not yet been examined.

Lung cancer and fibre type

41 As was the case at the time of our previous report, no data have been published from which it is possible to relate dust-exposure measurements for *crocidolite* in the absence of other types of asbestos to the risks of lung cancer. Weill and his colleagues studied men engaged in the production of asbestos cement in two factories, in one of which there was exposure to crocidolite in addition to chrysotile during the manufacture of pipes (Weill *et al*, 1979). They showed significantly raised mortality from lung cancer in their highest cumulative dust exposure group among those exposed to crocidolite, but not for those exposed to chrysotile alone. This result may or may not have been influenced by the fact that it was possible to confirm the living/dead status of only 75% of the workforce at the end of the follow-up period.*

42 A summary of all the published estimates of the slopes of the linear relationships between mortality from lung cancer and cumulative dose of fibre has been prepared in Table 6. According to Nicholson the lowest and highest values of the slopes for exposure to chrysotile alone are 0.06 to 5.3 and for mixed ex-

*The trace rate in this study is now reported to be 94% (Weill, personal communication).

posures 0.07 to 8.4. According to the calculations of Liddell the figures are 0.038 to 1.6 (chrysotile) and 0.06 to 2.7 (mixed). There is thus overlap between the estimated slopes for chrysotile and mixed exposures in both sets of calculations. In addition we have already referred to the study of British naval dockyard workers exposed to amphiboles and chrysotile in whom, although no dose-response relationship has been published, a deficiency of deaths from lung cancer was observed (Rossiter and Coles, 1980).

43 In the studies of female gas-mask makers exposed respectively to crocidolite and chrysotile already referred to (Acheson *et al*, 1982), the former experienced a significant excess of lung cancer mortality (13 observed, 6.2 expected) while the latter did not (6 observed, 4.8 expected). Although these women were comparable in terms of lapsed period, the duration of exposure may have been longer among those exposed to crocidolite and no measurements of dust levels are available from either factory.

44 As far as *amosite* is concerned an estimate of 35 fibres/ml for the average dust level in the insulation materials factory in New Jersey studied by Selikoff and his colleagues has recently been published (Nicholson, 1981). Using this figure Nicholson calculated that the mortality from lung cancer per fibre-year/ml may be substantially higher than for any group of workers exposed to chrysotile or to mixtures of chrysotile with amphiboles. It is worth noting that the dust estimate was derived during 1967, 1970 and 1971, not from the factory in question, but from two other factories operating the same process at a later date. Although Nicholson states that these plants "manufactured the same products from the same fibre type (amosite) to the same specifications and using the same type of machinery", it would seem unjustified to use uncritically their dust measurements for another factory which was in operation over 20 years previously during wartime conditions. Other reservations about this study are made later (para 76). The early experience of workers at a London factory where commercial amosite was used reveals a two-fold increase in mortality from lung cancer (57 observed, 29.1 expected), but no dust measurements are available prior to 1969 (Acheson *et al*, in press).

Asbestosis

45 In our previous report we commented on the paucity of data on the relationship of the frequency of asbestosis to fibre type for jobs of comparable dustiness. So far as we are aware nothing relevant to this issue has subsequently been published.

Summary

Mesothelioma

46 *Peritoneal* mesothelioma has an almost exclusive relationship with exposure to the amphiboles crocidolite and amosite,* but within the categories of workers exposed to these fibres there are large variations in the estimated life risk which reflect the influence of other factors, some of which are unknown. As far as *pleural* mesothelioma is concerned, although the association with amphiboles is less strong than for peritoneal mesothelioma and such tumours have been caused by exposure to chrysotile alone, all the recent publications that we have been able to find support our previous view that crocidolite is substantially more dangerous than chrysotile. A single relevant study published subsequently (Acheson *et al*, 1981), and updating of previously published results (Seidman *et al*, 1979; Selikoff *et al*, 1979), support the view that, in process work and among insulators, exposure to commercial amosite may confer as great a risk as crocidolite, or at least a risk intermediate between those of chrysotile and crocidolite.

Lung cancer

47 Where data are available which make possible a direct comparison within a single study (Weill *et al*, 1979) they support our previous view, that crocidolite and amosite at a given dust exposure level may be more dangerous than chrysotile. However, when comparisons are made between the slopes of the dose-response curves of studies of various populations of asbestos workers, no clear distinction can be found between the experience of those exposed to chrysotile and those exposed to mixtures (see Table 6). On the basis of the evidence now available it cannot be assumed that dose for dose chrysotile is in all circumstances necessarily safer than mixtures with amphiboles in respect of lung cancer.

Asbestosis

48 No recent relevant data have been found.

49 In our previous report we concluded the relevant section with a proviso based on the animal work which we regard as sufficiently important to reproduce in full here.

50 *"In view of the fact that it seems clear from animal work that all fibre types have the potential to produce the three main types of asbestos-related disease to a similar extent if the physical conditions of the dust cloud are appropriate, it follows that any change in industrial practice in the direction of the production of more finely dispersed fibre may be significant to health. This work suggests that, should commercial chrysotile be milled in such a way that it approaches the respirability of crocidolite and amosite, particularly if long (10—80μ) and extremely thin (<2.5μ) fibres are produced, the morbidity gradient in favour of chrysotile seen up to the present and discussed in this chapter may disappear in the future. In considering the possible future significance to health of such a trend it is necessary to balance the very much greater consumption of chrysotile than of the*

* We are aware of one case reported in association with chrysotile (Dement *et al*, 1982; McDonald *et al*, unpublished a).

amphiboles (Table 1, Fig 2) against the considerable improvements which have undoubtedly been secured in dust control in many areas in recent years. Changes in the range of usage of asbestos and any effects these would have on the accessibility of the fibre to human contact would also have to be taken into account" (para 168).

51 In the light of subsequent animal work, fibres of length $< 10\mu$ with high aspect ratio may also be relevant (Bertrand and Pezerat, 1980).

52 The differences in the risk of mesothelioma that we attribute to the three mineralogical types of asbestos do not necessarily reflect chemical differences. They may well reflect differences in the distribution of fibres of various configurations in the dust cloud not detected by current methods of measurement.

53 Walton (1982) has deduced from the data of Hwang and Gibbs (1981) that people who have worked with crocidolite have probably been exposed to substantially higher concentrations of fibres in the carcinogenic range of particle size than those exposed to other varieties of asbestos and that most of these fibres are not visible to the optical microscope.

Dose-response relationships

54 *We reviewed the main sources of the considerable uncertainty relating to historical dust measurements upon which dose-response relationships depend, stressed the dangers in converting particle counts to fibre counts (all British as well as all North American data prior to about 1964 were recorded in particles), and noted that the introduction of the 'eye-piece graticule' and personal as opposed to static sampling may have resulted in a DE FACTO tightening of the hygiene standard of 2 fibres/ml since its introduction in 1969.*

55 *With regard to asbestosis we drew attention to the special difficulties of definition in calibrating response to exposure in this condition. Although the data did not agree on this point we concluded that there was no evidence of a safe threshold in respect to chrysotile (except for certified asbestosis), and that the data from the only available longitudinal study were compatible with a linear relationship between incidence and dose. No data were available to study the relationship of dose to the frequency of asbestosis for crocidolite or amosite. We concluded that the fibrogenic effect of the fibre used at Rochdale had been underestimated, but this had been mitigated at least in part by the fact that the hygiene standard is currently enforced with more sensitive instruments and from personal samples taken in the breathing space of workers.*

56 *For LUNG CANCER, quantitative data from which the shape of a dose-response relationship could be determined were limited to Quebec chrysotile miners and millers and retired New Jersey asbestos workers. In both sets of data we found no evidence for a threshold of dose of dust below which there was no increment in risk, and formal statistical tests showed that the data were suitably described by straight lines.*

57 *For AMOSITE and CROCIDOLITE no quantitative data from which the shape of the dose-response relationship could be deduced were available.*

58 *For MESOTHELIOMA, although quantitative dust measurements are limited to one group of workers, these and semi-quantitative data strongly suggest that the risk of these tumours increases with increasing dose (paras 169—214).*

Up-date

Asbestosis

59 The British Occupational Hygiene Society (BOHS) Committee on Asbestos has recently published a further report on morbidity (BOHS, 1983). It contains data on a reconstituted study population all of whom started work in a factory after 1950, and so have been employed during the years for which dust measurements, which started in 1951, are available. The cohort included 295 men with medical records, who had no known exposure to asbestos dust prior to employment in the factory, and who had completed 10 years' (not necessarily continuous) work with asbestos in the factory by 31 December, 1976. Efforts were made to trace 130 of the 295 men who had left the factory by the end of 1976 (excluding 28 known to have died) so that they could return for an X-ray and clinical examination.

60 Radiological and clinical data were used to establish the presence (or absence) of seven "adverse effects" according to the criteria shown in Table 5. These included the occurrence of parenchymal and pleural abnormalities, changes in lung function, and the appearance of "chest sounds" (including crepitations). By far the most frequent adverse effect was a value of $FEV_1/FVC < 0.70$, which was found in 111 men, while the frequencies of the other adverse effects ranged from 22 to 34. Without considering dust exposure level, 163 (55%) of the 295 men had at least one of the adverse effects, and 52 (18%) had an effect other than $FEV_1/FVC < 0.70$. Estimates of the probabilities of each (or any one) of these adverse effects occurring in relation to the cumulative dose of fibre were made. For a cumulative dose of 50 fibre-years/ml it was estimated that about 7% of persons may be expected to have at least one effect, with

about 2% for effects B, E and F, under 2% for effect G (chest sounds including crepitations), and under 1% for effects A and D (no data are given on effect C). In this study the dust levels are presented in terms of modern instruments, after a very detailed comparison of the different measurement techniques used between 1951 and 1976 had been carried out, but related to static, not personal, sampling.

61 In our previous review we dealt in some detail with the differences between the two previously reported morbidity studies (BOHS, 1968; Berry *et al*, 1979). In the new study more men were included who had been exposed to lower concentrations of dust. On the other hand the maximum duration of follow-up is at present less than 30 years since first employment. From the most recent of the two earlier studies, in which men who had left employment were also included, the estimated proportion with crepitations by 25 fibre-years/ml (equivalent to 50 fibre-years/ml by modern counting methods with static sampling) was almost negligible. In the present study the estimated comparable figure (for adverse effect G) was under 2%. If one takes the view that personal, rather than static, sampling doubles the measured exposure levels, then enforcing a control limit of 1 fibre/ml with personal sampling devices might result in less than 1% of persons developing adverse effect G, and less than 2% of persons developing at least one of the seven effects over 50 years' employment. These proportions have been estimated from Figs 10 and 11 of the latest BOHS report (1983).

62 The authors of this study point out that the adverse effects are not necessarily attributable to asbestos. In particular, the inclusion of $FEV_1/FVC < 0.70$ as an index of adverse effect is debatable, and the authors themselves state that "it did not correlate with dust exposure and this bears out the latest thinking that $FEV_1/FVC < 0.70$ is an inappropriate criterion of an adverse effect of asbestos. It is well known, for example, that smokers develop a reduced FEV_1/FVC and there were many smokers in the populations studied." To be certain of the extent to which these changes are independent of age, smoking and other confounding factors it would be necessary to make comparisons with a control group of men not exposed to asbestos. An extended discussion of these adverse effects is given in Appendix C.

63 It is noted that the composition of the cohort for the new BOHS study (BOHS 1983) is similar in definition and size to the group investigated by Morris (see Appendix A).

64 In a study of the mortality of workers certified by pneumoconiosis medical panels as having asbestosis, Berry (1981) has shown that the excess lung cancer rate and the mesothelioma and asbestosis rates all increased with percentage disability.

Lung cancer

65 Since our previous report was published a large number of papers have appeared which include estimates of individual dust exposure levels. We have also traced many studies among different groups of workers where linear dose-response relationships provide a satisfactory description of the association between mortality from lung cancer and cumulative dose of asbestos, compared to the three available in 1978. The concept of a linear relationship now seems to be generally accepted by most of the authors in describing their own data, and in the various summaries that have been made, although not without reservations (Peto, 1978, 1979; Acheson and Gardner, 1979a; McDonald *et al*, 1980a; Enterline, 1981; Nicholson, 1981; Selikoff, 1981; Dement *et al*, 1982; Liddell, 1982; McDonald *et al*, unpublished a and b).

66 Quantitative studies of the relationship of dust exposure to mortality from lung cancer have now been reported in miners and millers of chrysotile asbestos, workers in the production industry manufacturing textiles, friction materials and cement, and maintenance workers. In more detail, they are:

1 Quebec chrysotile miners and millers (McDonald *et al*, 1980b),
2 Thetford Mines chrysotile miners and millers (Nicholson *et al*, 1979),
3 New Jersey factory workers manufacturing products from chrysotile (Henderson and Enterline, 1979),
4 New Jersey factory workers manufacturing products from chrysotile (Nicholson *et al*, 1981),
5 New Jersey maintenance workers exposed to chrysotile, amosite and crocidolite (Henderson and Enterline, 1979),
6 UK factory workers manufacturing textiles from chrysotile and some crocidolite (Peto, 1980a),
7 South Carolina factory workers manufacturing textiles from chrysotile (Dement *et al*, 1982),
8 South Carolina factory workers manufacturing textiles from chrysotile (McDonald *et al*, unpublished a),
9 UK factory workers manufacturing friction materials containing chrysotile and some crocidolite (Berry and Newhouse, 1983),
10 New Orleans factory workers manufacturing asbestos cement products containing chrysotile and some crocidolite (Weill *et al*, 1979),
11 Pennsylvania factory workers manufacturing textiles using chrysotile, amosite and crocidolite (McDonald *et al*, unpublished b),
12 Canadian factory workers manufacturing asbestos cement containing amosite and chrysotile (Finklestein, 1982).

67 Study 2 (which was not based on individual exposures) is an investigation of a sub-group of study 1, with study 4 (again not based on individual exposures) being similarly related to study 3, and study 7 to study 8.

68 The twelve studies mentioned above have been based on estimations of the cumulative exposures of individual workers (except for studies 2 and 4) either for the complete cohort or on a case-control basis. Some of the difficulties inherent in the available dust measurements and in this index as a measure of biological dose, in addition to the problems of appropriately measuring the response (mortality), were discussed in our previous report. These are repeated in Appendix D, together with some further points which apply to some of the more recent studies, and should continue to be borne in mind. The cumulative dose, however, is still the method of presentation of results with regard to dust levels used in the literature, and so our arguments are in these terms. However, because of different modes of accumulation in different studies, sometimes including exposures to age 45, or during the first 20 years of employment, or to death etc, comparison between results is further complicated.

69 In addition, a number of other relationships have appeared which have incorporated estimated exposures of groups of workers in a similar way to studies 2 and 4, using either an average dust level together with duration of work or assigning numerical dust values to previously used qualitative assessments (for example, "low to moderate", "severe") of degree of exposure. Studies treated in this way have been:

13 UK factory workers manufacturing a number of products containing chrysotile, crocidolite and amosite (Newhouse and Berry, 1979),

14 US factory workers manufacturing insulation products containing amosite (Seidman *et al*, 1979),

15 US insulation workers exposed to amosite and chrysotile (Selikoff *et al*, 1979).

70 We used earlier published results from studies 1, 3 and 5 in our previous review. Study 6 was also included, but only an overall SMR from lung cancer and an average cumulative dose were available, with linearity being assumed.

71 For some of the studies mentioned above the slopes of the dose-response relationships have been estimated and tabulated by Nicholson (1981) and repeated by Selikoff (1981) and Liddell (1982). We have collated their figures into Table 6, and have given our previously estimated slopes together with those of the original authors if provided. It is important to note that the slopes given by Nicholson and our own previous values are from straight lines of the form:

$$SMR = 100 + b \times D,$$

where SMR = the Standardised Mortality Ratio, b = the slope of the line, and D = the cumulative dose in fibre-years/ml of asbestos. By contrast those given by Liddell are usually from straight lines of the form:

$$RR = 1 + \frac{b}{100} \times D,$$

where RR = the Relative Risk compared to unexposed persons.

72 The essential difference between these two approaches, and vital to their interpretation, is that in the former the line is constrained to pass through an SMR of 100 at zero exposure (D = 0). For each of the studies where SMRs were calculated based on an external standard, this constraint is tantamount to assuming that the chosen standard population was appropriate. In other words it is assumed that the standard population and the asbestos workers had a similar experience in respect of all factors other than exposure to asbestos (including smoking) with a bearing on the incidence of lung cancer. It is unlikely that this will have been true in any particular study, and the relative risk approach allows that the SMR at zero exposure may be different from 100, say SMR_0. The relative risk at any exposure level D is thus obtained as SMR_D/SMR_0, so that if there is a linear relationship with dose of slope b′, then:

$$SMR_D = SMR_0 + b' \times D$$

This leads to:

$$RR_D = 1 + \frac{b^*}{100} \times D,$$

where $b^* = 100b'/SMR_0$ is similarly scaled for comparison purposes to the slope b above. Before each of our earlier slope estimates (Acheson and Gardner, 1979a) for studies 1, 3 and 5, we carried out a formal statistical test (using a weighted regression analysis) of the intercept on the SMR axis and found no reason to suggest that 100 was inappropriate. In his review Liddell (1982) found that 100 was inappropriate for several of the recently published dose-response relationships. For studies analysed on a case-control (case-referent) basis the slope of the relationship between relative risk and cumulative dose is determined more directly, without the involvement of an external standard population.

73 The slope estimates shown in Table 6 have sizeable sampling errors attached to them; for example, Liddell (1982) quotes a 90% confidence interval of from 0.016 to 0.069 for the value of 0.038 in chrysotile miners (although this is based on the largest number of lung cancer deaths in all the studies) and this should be borne in mind. A possible reason why Liddell's estimated slopes are much lower than those of Nicholson (e.g. studies 7, 13 and 14) is that the populations used for comparison had a more favourable experience than the workforce under consideration in respect of other carcinogens with a bearing on the incidence of lung cancer, e.g. smoking habits. If this were so the effect would be to raise the calcu-

ted SMR at zero exposure and reduce the gradient f the slope (Figs 2 and 3). We prefer the relative risk pproach because it does not involve any assumption bout the appropriateness of the standard population nd also describes the empirical data more closely.

74 The studies shown in Table 6 have been listed so that those where exposure was only, or principally, to chrysotile are given first, and those where amphiboles were used are given later. It is clear, whichever of the sets of estimated slopes by either Nicholson or Liddell are taken, that there are considerable differences in the slopes of the lines found in the various studies. The variation in Nicholson's (0.06 to 9.1) is greater than in those calculated by Liddell (0.038 to 2.7). Without exception wherever estimates of slopes were made by Liddell they were lower than those of Nicholson. Among the studies of persons exposed to chrysotile only, there are low estimated slopes for miners and millers in Quebec and steep slopes for textile workers in South Carolina. Men who entered the Rochdale textile factory after 1951 and were exposed to asbestos for at least 10 years (study 6L), women employed at Barking (study 13F) and men employed during and immediately after the second world war in the manufacture of amosite-containing insulation products (study 14) all experienced a steep relationship between dose of fibre and lung cancer mortality.

75 With regard to the Rochdale results, the finding of higher mortality in more recent employees (Peto, 1980a) has now lessened, and was probably due to the small number of deaths at that time (Peto J, personal communication). The figures at Barking are based on estimated group exposures (5 to 10 fibres/ml for "low to moderate" exposed groups and 20 fibres/ml or higher before 1945 for the groups with "severe" exposure; Nicholson, 1981) in a situation where no individual dust measurements were available, and the number of employed women was small. It must be seriously questioned as to whether or not these estimated figures have any real meaning.

76 With respect to the exceptionally high slope in amosite factory workers reported by Nicholson (1981), at least two points are relevant. The first, relating to the relevance of the estimated dust levels, has already been pointed out (para 44). Secondly, the SMRs from lung cancer for men employed for very short durations of time (up to three months) are markedly raised (between 275 and 300) as we discussed in our earlier report (see present Fig 2; and Fig 13 in Acheson and Gardner, 1979a). Nicholson apparently takes the view that the external standard is nonetheless appropriate and fits a line with an SMR of 100 at zero exposure (see Fig 2); Liddell has doubts about the appropriateness of the death rates of the general population of the State of New Jersey as a standard for these factory workers, and consequently reports a slope for the relative risk which is much less steep (see Fig 2).

77 The interpretation of the slope of the dose-response relationship in the South Carolina textile factory is of particular importance because it is by far the steepest attributed to the effects of chrysotile, and chrysotile is now for practical purposes the only type of asbestos fibre imported into the UK (Table 1). In both the first study from this factory, of a limited cohort of white males employed for at least six months (Dement *et al*, 1982)*, and in a second study of the whole workforce (McDonald *et al*, unpublished a) steep slopes were reported by Liddell (1982). From Fig 2 of McDonald *et al* (unpublished a), slopes of 2.3 and 1.7 respectively for the relative risks from the two studies can be derived by applying a conversion factor of 3 for million particles per cubic foot to fibres per ml. Since Liddell estimates an SMR of 161 at zero exposure from the data of Dement *et al* (1982), the slope of the relationship between the SMR and cumulative dose (in fibre-years/ml) is thus $1.61 \times 2.3 = 3.7$. This is the value we have used in Fig 3, and it is similar to that (of 4.0) derived from Fig 2 of Dement *et al* (1982) (see Table 6).

78 In their lowest exposure group at dust levels up to 27.4 fibres-year/ml, Dement and his co-workers found an SMR of 223. A plot of their data (see Fig 3) suggests that the use of the US national rate as a standard may have been inappropriate and that the expected numbers of deaths are therefore too low. However, it is only fair to state that the authors themselves do not agree. If they had based their expected numbers on local mortality rates the SMRs for lung cancer would have been much lower than the published figures, because the county in which the factory was situated had a remarkably high mortality from lung cancer in men; 75% above the national average. Although Dement and his colleagues (1982) attribute this to the presence of a large number of ex-shipyard workers who had worked in wartime naval construction, the *Atlas of Cancer Mortality for US Counties* (Mason *et al*, 1975) shows that the lung cancer mortality rates in women are also significantly high in this county, a finding unlikely to be due to shipyard work. Even though women were employed in the shipyards, the numbers involved were small (Blot *et al*, 1979). Smoking does not seem to be responsible, as the smoking habits of members of the workforce were similar to those of the adult population of the US. There remains the possibility that the population of this county have been exposed to an unknown carcinogen which explains in part the excess mortality from lung cancer experienced by the workforce when compared with the US population as a whole.

79 If one regards the standard population as suitable and forces the line through the origin (as does Nicholson) the slope becomes much steeper (5.3 contrasted with 2.3). Even if one were to reject the value

*A further study of men employed in this factory for at least one month which does not alter the conclusions has recently been published (Dement *et al*, 1983).

of 5.3, the lower figure is still appreciably higher than for other chrysotile (or predominantly chrysotile) applications, including mining and milling (studies 1 and 2), manufacture of textiles (study 6) and friction materials (study 9) in the UK, asbestos cement production (study 10) and the manufacture of assorted products (studies 3 and 4).

80 In all the studies discussed in this section a major consideration to bear in mind is the validity of the exposure data. These are based almost completely on measurements made in terms of particles of dust collected from static sampling points (and, prior to about 1965, not on fibre counts) and it has been necessary to convert concentrations originally in millions of particles per cubic foot to fibres/ml in order to make the data relate to modern hygiene standards (which are based on fibres/ml). Both the use of data from non-fibre-specific techniques based on outmoded methods which differed in different countries, and the incorporation of conversion factors which are at the best arguable introduce major uncertainties, especially when similar assumptions are applied to such different environments as mining and textile manufacture. A conversion factor of 3 fibres/ml to 1 million particles/cubic foot, a value in the middle of the range considered in our previous report, has been used for chrysotile miners and millers by McDonald *et al* (1980a), for textile workers (except for the preparation area where a conversion factor of 8 was used) by Dement *et al* (1982) and by Nicholson (1981). McDonald *et al* (unpublished a) consider an average figure of 6 to be more appropriate for the South Carolina textile plant, and quote a range of from 1.3 to 10.0 for different areas of the plant. On the basis of the high mortality from asbestosis in this plant, Weill (1982) has challenged the validity of the dust measurements in the South Carolina textile factory and has suggested that the early dust levels may have been underestimated. This is also the view of Steel (1983), whose comments are reproduced as Appendix B to this report.

Cigarette smoking and asbestos

81 The evidence on the synergism between asbestos and cigarette smoking in lung cancer which has recently become available suggests that this may be intermediate between an additive and multiplicative effect, with a smaller than multiplicative interaction term (Berry, 1980; Selikoff *et al*, 1980; Saracci, 1981; Acheson *et al*, in press). An interaction of this form has a modifying influence on the slope of a linear dose-response relationship, namely, to increase the observed slope above that which would be found in the absence of an interaction (or in the absence of cigarette smoking). Moreover, if the smoking habits of the industrial cohort are greater than in the standard comparison population the effect will be similar and will exaggerate the slope of the dose-response curve (Acheson and Gardner, 1981; Gardner, 1983b). For these reasons a further note of caution should be struck in relation to many of the dose-response curves in Table 6, as smoking habits were studied in few of them.

82 The likely reduction in the incidence of lung cancer among asbestos exposed persons who cease smoking cigarettes is discussed by Selikoff *et al* (1980) and Saracci (1981), and the latter suggests that over 90% of the excess lung cancer deaths may thus be prevented.

Mesothelioma

83 As far as mesothelioma is concerned one of the important findings has been that the incidence appears to be related to between the third and fourth power of the lapsed time since beginning exposure (Peto *et al*, 1982). In specific terms:

$$I_t = b.t^k$$

where I_t = incidence t years after initial exposure, k = a numerical constant between 3 and 4, and b is another constant which is possibly dependent upon a number of factors including fibre type, duration and intensity of exposure, age and site. Peto and his coworkers have shown that for five different cohorts of asbestos workers, where the data had been published in a form suitable for analysis, a value of k = 3.2 gave a satisfactory fit in each case.

84 Apart from McDonald *et al*'s data quoted in our previous report (Table 31X) no quantitative information is available about the relationship of the incidence of mesothelioma to dust exposure. However, subsequently published semi-quantitative data support the conclusion that the risk increases with increasing intensity and duration of exposure (Hobbs *et al*, 1980). At present nothing is known about the risk of mesothelioma as compared to lung cancer at a given level of exposure to asbestos.

Implications for the industrial control limit

Crocidolite

85 *We concluded that contact between man and crocidolite should be limited to the minimum practicable, that its importation should be prohibited, and that stringent regulations should continue to be applied to protect workers and the public in respect of crocidolite-containing materials.*

Amosite

86 *We concluded that although strictly quantitative data were lacking, the evidence suggested strongly that this material had been more dangerous than chrysotile. Therefore a stricter control limit might be appropriate.*

Chrysotile

Asbestosis

87 *We compared two studies from Rochdale and concluded that, if modern techniques used to enforce the standard are two to five times more sensitive than those used to arrive at measurements in the 1950s and 1960s the evidence for a cumulative incidence of 1% asbestosis occurring after a life-time's exposure at 2 fibres/ml (as currently enforced) fell away.*

Lung cancer

88 *Basing our calculations on a linear dose/response relationship without threshold and using various conversion factors for particles/fibres and old/new measurement techniques we produced an array of possible control limits at which a particular excess mortality of asbestos-related disease might occur. We concluded that, for example, an excess mortality from asbestos-related disease of 2% might be associated with any point in a range of from 5 fibres/ml to 0.4 fibres/ml, and that bearing in mind the very considerable uncertainties a figure towards the lower end of the array might represent an appropriate compromise (paras 242—259).*

Up-date

Crocidolite

89 No subsequent data have been published which suggest we should modify our conclusion.

Amosite

90 Subsequent data strengthen our conclusion that amosite is probably more dangerous than chrysotile (see paras 40 and 44). In the light of the gross reduction in imports resulting from its replacement in the production of insulation board, formal prohibition of new products might be considered.

91 Since the amphiboles are of less relevance in terms of imports and manufactured products now than they were at the time of our earlier report, our discussion of the control limit is focused on chrysotile. This does not preclude the need for careful restrictions on the handling and uses of materials containing crocidolite or amosite, including their maintenance, repair or demolition, for which provision already exists.

Chrysotile

92 Our earlier recommendations for chrysotile were based on the following assumptions:

(a) that there is a linear relationship without threshold between cumulative exposure to chrysotile and lung cancer mortality;

(b) that in populations exposed to chrysotile the numbers of excess deaths from lung cancer and from asbestosis have been similar;

(c) that mesothelioma deaths were rare from exposure to chrysotile alone;

(d) that, from the latest morbidity data related to cumulative exposure from Rochdale then available, the evidence (after taking into consideration personal sampling with modern instruments) in favour of a material prevalence of asbestosis occurring after a lifetime's work at the control limit as enforced in 1979 was slight.

93 Nothing has been published since our report which leads us to wish to vary our first three assumptions. In relation to the second assumption McDonald *et al* (unpublished a) report 21 deaths from "pneumoconiosis" and 29.4 excess deaths from lung cancer in the South Caroline chrysotile textile factory.

94 We wish to point out that this and other similar figures relate to past exposures to asbestos dust which were higher than those likely to be encountered today or in the future. As asbestosis is particularly associated with high exposure levels our second assumption is conservative and incorporates a safety factor into a control limit based on this approach.

95 The final assumption merits further discussion in view of the recent BOHS survey of morbidity in relation to dust measurements (BOHS, 1983). The probability of at least one of seven adverse effects developing in an individual was estimated to be 7% after the equivalent 50 years' exposure to the control limit of 1 fibre/ml, when static sampling was used. If it were to be accepted, as was not the case by the authors of the latest BOHS report, that measurements based on personal samplers are on average twice as high as those based on static samplers (Acheson and Gardner, 1979a; Steel, 1979), the estimated prevalence of at least one of seven adverse effects would be lowered to less than 2%. In either case a view has to be taken on which of the seven adverse effects are indicators of serious morbidity and also to what extent they are asbestos-related. We tend to take the position that, although the present estimates of adverse effects at any level of cumulative exposure appear to be higher than in the previous BOHS studies, the extent to which some of these effects, notably the commonest, F, are related to exposure to asbestos is questionable.

Revised estimates for lung cancer

96 The major difficulties concerning the use and interpretation of past exposure levels in the construction of dose-response relationships, which we reviewed in our previous report and elsewhere (Acheson and Gardner, 1980b) and have referred to in para 68 and Appendix D of this paper, remain. We previously took a range of conversion factors (1, 2 and 5) from million particles per cubic foot to fibres per ml, and recent papers have followed an average figure of 3 suggested as appropriate to chrysotile miners and millers (McDonald *et al*, 1980a), although there was much variation of this factor between sites, and textile workers in South Carolina (Dement *et al*, 1982). The introduction of the eyepiece graticule method of counting around 1974 had the effect that more fibres

were counted per area of slide by a factor of about 2, and so implied that past counts should be approximately doubled to compare them with results from techniques used to enforce the control limit today (Steel, 1979). The determination of a suitable conversion factor between personal and static sampling is undoubtedly complicated by the fact that some individual exposures are lower when measured by personal sampling, but they are in the minority (Steel, 1979; BOHS, 1983). In general, it appears that concentrations obtained from personal samplers are higher than for static samplers, and that a factor of 2 may be an accepted compromise. An exception to this comes from the results of a study at Rochdale in 1971, where dust levels from one set of personal samplers were found to be lower than average levels from static samplers collected over a period of one year for nearly all processes (Smither and Lewinsohn, 1973)*.

97 As far as lung cancer is concerned, recent publications imply that the range of excess mortality associated with exposure to chrysotile is greater than had previously been reported. Thus, studies from the South Carolina textile factory indicate a much steeper dose-response relationship than any earlier study, while at the other extreme a large British workforce making friction materials experienced no excess mortality from lung cancer (149 observed, 151 expected) and there is doubt as to whether there is a positive dose-response relationship (see Table 6). A study of an asbestos cement factory in Wales also showed no excess mortality (30 observed, 33 expected), but no attempt was made in the analysis to look at the dose-response relationship. More information is urgently needed about the occurrence of asbestos-related disease in the asbestos cement industry where chrysotile only has been used, particularly in view of the fact that this is the largest single application of chrysotile in the UK (Table 2).

98 Using the various slopes of the linear dose-response relationships given in Table 6 it is possible, adopting the same approach as in our earlier report, to estimate fibre concentrations which after 50 years' exposure might be associated with varying levels of excess mortality from lung cancer. These are shown in Table 7 for various proportions (relative to all deaths) of extra deaths due to lung cancer. The lowest fibre levels associated with a given level of mortality are given by the textile factory in South Carolina. According to Nicholson's estimate of the slope, 1% extra deaths from cancer of the lung would occur after a working lifetime's exposure to a dust level of 0.04 fibres/ml (one twenty-fifth of the current UK control limit). A similar proportion of extra lung cancer deaths would result from a rather higher dust level (0.09 fibres/ml) if Liddell's method (which we prefer for the reasons stated in para 73) is followed.

*There are also thought to be problems with the manner in which the personal samples were collected in this study (Steel, J personal communication).

If a conversion factor of 6, rather than 3, is used (as suggested for this factory by McDonald *et al*, unpublished a) the relative risk method of calculation yields an associated dust level of 0.17 fibres/ml. Table 7 shows that the range of fibre concentrations that would produce an excess of lung cancer of 1% is from 0.04 to 5.0 fibres/ml. The highest dust levels compatible with a given level of excess mortality are those derived from miners and millers and the manufacture of friction materials, the lowest from textile manufacture.

99 If it were agreed that the effect of the introduction of new counting techniques and personal sampling instruments had increased the measured fibre concentrations by a multiple of between 2 and 5 (Acheson and Gardner, 1979a), then the figures shown in the body of Table 7 would be increased accordingly. Looked at another way, the excess deaths from lung cancer associated with exposure to 1 fibre/ml for 50 years range from 0.2% to 27% (see Table 24a in Advisory Committee on Asbestos, 1979), which would be reduced by a factor of between 2 and 5 to take account of modern counting and personal sampling. The weight given to the different figures depends upon various technical considerations relating to the calculations, such as the validity of the dust estimates and of the standard populations used in the comparisons which have already been discussed.

100 Other points that should be taken into account in the interpretation of these figures are that the control limit in practice is intended to be a maximum value and that the average exposure will be less, perhaps as little as one-tenth of the control limit (see Appendix M in Advisory Committee on Asbestos, 1979). Furthermore, with increasing mobility of labour it is becoming usual for the workforce to leave very much earlier than with 50 years' exposure, although they may move to other asbestos-using employment. There are also questions outside the scientific data, relating to policy, cost etc which need to be considered in setting a control limit (Duncan, 1981).

101 In view of the wide range of values displayed in Table 7 the question must arise whether it is rational to employ a single control limit for chrysotile throughout industry (McDonald, 1982). To employ a single control limit might either put certain categories of workers (for example, those in textiles) at risk if the limit were at one end of the spectrum, or if the control limit were at the other extreme place an unnecessary and possibly insupportable burden of cost on others (for example, manufacturers of friction materials). A further complication is that for large sectors of the industry, such as asbestos cement and tiles (which together consume about half of all imports of chrysotile), and for miscellaneous uses and for persons who utilise asbestos products, no dose-response data have been collected. Such data as are available suggest that the manufacture of asbestos cement products from chrysotile may have been as-

sociated with relatively little excess mortality, but more information is urgently needed on this point.

102 Epidemiological data which have been published since our last report suggest that the manufacture of textiles from chrysotile may have been more dangerous than was previously recognised, and that it might therefore be prudent to recommend stricter control in this part of the industry than for the remainder. However, it should be borne in mind that uncertainties remain concerning both the validity of the historical dust measurements and the external mortality standard used in the relevant study (see paras 75 to 80). Textile production only accounts for about 4% of the British asbestos industry (Table 2).

103 Studies published from other parts of the industry do not suggest the need for a reduction in the control limit. Nevertheless, as was indicated in Advisory Committee on Asbestos (1979), in view of the fact that all forms of asbestos can be carcinogenic, further reductions in the control limit should be made whenever advances in engineering make them reasonably practicable, and the use of all types of asbestos should be curtailed as safe and effective substitutes become available.

104 Public policy should take account of the fact that all types of asbestos are extremely durable and that products containing them may require further processing, including servicing and demolition, in circumstances where dust control may be difficult and far removed in place and time from the original production process.

Conclusions

105 In the light of our terms of reference (paras 1 and 2) we conclude as follows:

(a) we have not found any material which was available to the Advisory Committee on Asbestos which on reconsideration would have altered the conclusions in our previous report;

(b) data which have become available subsequently lead us to alter the conclusion of our previous report in so far as they relate to the control limit in the workplace as follows:

(i) amosite imports have effectively ceased and chrysotile is at present for practical purposes the only type of raw asbestos fibre imported into the UK;

(ii) the evidence that asbestos fibre causes alimentary tract cancer in man is less convincing than in 1979;

(iii) the case that amosite is more dangerous than chrysotile has strengthened in respect of both peritoneal and pleural mesothelioma. We recommend that formal prohibition of the manufacture and importation of new products made of amosite and crocidolite should be considered;

(iv) the range in the slopes of the dose-response relationships for lung cancer and chrysotile exposure has widened since our report of 1979. At one extreme the risk associated with the manufacture of textiles in South Carolina may have been greater than has been previously reported in relation to any other chrysotile application, while at the other extreme the presence of any increased risk with increasing exposure in a large cohort of men who manufactured brake linings is questionable.

106 We consider that subsequent evidence has supported the view expressed in 1979 that in respect of lung cancer the relationship of exposure to mortality is linear.

107 Subsequent evidence has supported our previous view that peritoneal mesothelioma for practical purposes never, and pleural mesothelioma rarely, has occurred in man in relation to exposure to chrysotile alone.

108 In view of the fact that all forms of asbestos can be carcinogenic, further improvements in control should be made as advances in engineering make them reasonably practicable and the use of all types of asbestos should be curtailed as safer and effective substitutes become available.

109 Steps should be taken to ensure that measurements of exposure to asbestos in the workplace are made and recorded in such a way that it is possible to determine what benefits (if any) have occurred as a result of improvements in control of dust.

110 We draw attention to the fact that little epidemiological information is available about the effects of work in the asbestos cement industry where chrysotile only has been used. As this is now the largest single section of the asbestos industry in the UK, further research should be carried out at the earliest opportunity.

Appendix A

Review of report by Dr J G Morris

111 The report by Morris was dated 24 February 1978 and was circulated to members of the Medical Working Group of the Advisory Committee on Asbestos in April of that year. The papers comprised a brief description of a further study of the incidence of disease in a group of men who had been exposed to asbestos dust at TBA (Rochdale), carried out by the Medical and Health Physics Department of the factory in 1977; an appendix (Appendix I) describing methods of dust measurement at TBA by Dr A L

Rickards; an appendix (Appendix II) describing criteria of adverse effects; some graphs; a specimen proforma for recording clinical data; and an enciphered summary of the clinical and dust information for the 286 men in the cohort.

112 The cohort consisted of men who had been first employed at TBA Rochdale after 1 January 1951 and who had completed 10 years of service by 31 December 1976. Men with known industrial exposure to asbestos outside TBA either pre- or post-1951 were excluded from the study. According to Morris the study was undertaken "because of the pressing need to know whether the present 2 fibres-year/cm³ was in fact a safe standard or not in view of public, governmental, union and management anxiety". Many of the men in the cohort had also been included in a study carried out on behalf of BOHS by Berry *et al* (1979), which was reviewed in detail by the present authors in their 1979 report. Berry *et al*'s data related to 379 men employed in the same factory who had worked for at least 10 years between 1 January 1933 and 31 December 1972. Of these 379 men, 197 were first employed after 1951 and will presumably have been included in the 286 men studied by Morris.

113 Morris's data differ from those of Berry *et al* in the definition of adverse effects and in a number of other particulars, notably that re-examination of as many of the men as possible was undertaken and a further attempt was made to date the occurrence of the first adverse effect by review of clinical records and X-rays. The dust measurements which Morris uses are those prepared by Rickards. For the period 1951—74 they are based on static sampling, subsequently on personal sampling. Rickards has converted the data "to modern membrane filter values expressed as fibres per ml".

114 Morris's results show during the period 1976—77 that 66 (23%) of the 286 persons were identified as having an adverse effect defined as one or more of the following criteria: crepitations, radiological changes, lung function tests (including gas transfer and K factor), clubbing, dyspnoea and other symptoms. An analysis of cumulative dust level against years of exposure suggested that the 66 men with adverse effects had experienced dust exposures at a rate greater than 2 fibre-years per ml.

115 In his report Morris offered to provide further information on the men he had studied. This offer was not taken up because it was decided that, in view of the decline in dust levels in industry, cancer mortality was likely in future to prove a more sensitive indicator of risk of asbestos-related disease than asbestosis and because there was a substantial degree of overlap between Morris's data and Berry's post-1951 material which had been dealt with in detail.

116 The recent BOHS Report (1983) reviewed in paras 59 to 63 describes an almost identical cohort in terms of similar criteria of adverse effect. The authors (EDA and MJG) of this paper visited Dr Morris in February 1983 to disucss the progress of his study. It remains in unpublished form, and it was agreed then that because of the substantial overlap with the BOHS (1983) report the findings would be similar.

Appendix B

Note by Dr J Steel on dust estimates in the South Carolina chrysotile textile factory

117 If we examine the sampling records reported by Dement *et al* (1982), it appears that from 1930 to 1945 about 12 atmospheric samples were obtained on average each year for the whole plant. As they were required for insurance purposes or for use by governmental health agencies, it is likely that the samples were collected annually by these organisations and the possibility exists that estimates of dust exposure within large areas of the plant are based on single samples taken once a year. If unrepresentative sampling locations were originally chosen, then large errors will have been introduced into the exposure estimates. Moreover, once the locations of the sampling stations were fixed, they would be unlikely to change from year to year and the errors would be perpetuated.

118 From 1945 to 1960, roughly the same low mean number of samples was taken annually, but samples were collected almost entirely by company personnel. In the potentially dusty operation of preparation/waste recovery, 1945 marks a watershed between high and much lower estimated mean exposure levels and while this change could be attributed to improved dust control, it might also be ascribed to a change in sampling personnel. The people involved in sampling from 1945 to 1960 would initially have little experience and expertise, and their motives and bias would be completely opposite to those of the agencies sampling during 1930 to 1945.

119 Relatively large numbers of air samples were taken over the period 1960 to 1975, but it is likely that most of these samples were obtained after 1971 when the membrane filter technique was used exclusively. Thus, if the possible sampling errors described above tended to produce low concentration figures for the relatively few measurements taken during the period 1930 to 1970, then this would result in a systematic underestimation of exposure over the major period of the study with consequent effects on the slope of the exposure-response line for lung cancer.

Appendix C

Note by Professor M Turner-Warwick on indices of adverse effects and asbestosis in the BOHS Committee on Asbestos study

120 Attempts to identify the earliest manifestations of asbestosis and thence their relationship to dust exposure levels have been considered recently in a report by the BOHS Committee on Asbestos (BOHS, 1983) and in a report on a closely similar cohort by Dr Morris. The BOHS used seven radiological, clinical and lung function criteria as adverse effects (see Table 5). These included five effects recorded as change between at least two measurements over the observation period; namely, the development or increase of parenchymal abnormalities, the development of pleural changes and abnormal change in various lung function measurements. Two other adverse effects were recorded if they were observed on the initial or subsequent examination; namely an FEV_1/FVC ratio of less than 0.70 or the presence of chest sounds (including crepitations, rales or crackles). In the cohort studied chest radiographs were taken and clinical examination made regularly over the period between 1951 and 1970 but lung function studies were only introduced in 1967 (Factory A) and 1960 (Factory B). Thus, information on four of seven adverse effects were not available for the first 10 to 17 years of the study. By far the most frequent adverse effect in the BOHS report was Factor F ($FEV_1/FVC < 0.70$) which accounted for 40% of all effect occurrences in Factory A and 34% in Factory B. It is difficult to assess the relevance of this measurement as an adverse effect (a) in the absence of lung function tests during the first 10 years of the study, (b) without information on the numbers having a reduced ratio at the time of initial examination, and (c) absence of detail on smoking.

121 The authors of this study themselves point out that the adverse effects are not necessarily attributable to asbestos. In particular, the inclusion of $FEV_1/FVC < 0.70$ as an index of adverse effect is debatable and as the authors stated: "it did not correlate with dust exposure" and "this bears out the latest thinking that $FEV_1/FVC < 0.70$ is an inappropriate criteria of an adverse effect of asbestos. It is well known, for example, that smokers develop a reduced FEV_1/FVC and there were many smokers in the population studied." To be certain of the extent to which these changes are independent of age and smoking and other confounding factors, it would be necessary to make comparisons with a control group of men not exposed to asbestos or to study workers at the beginning as well as after exposure.

122 Without considering dust exposure levels, 52 (18%) of 295 men at Factory A developed only adverse effects other than Factor F. Estimates of the probability of developing each or any one of these adverse effects in relation to the cumulative dose of fibre were made. For a cumulative dose of 50 fibre-years per ml it was estimated that about 2% of persons may be expected to develop effects B and E; under 2% factor G and under 1% for effects A and D. In this study, the dust levels are presented in terms of modern instruments after a very detailed comparison of the different measurement techniques used between 1951 and 1976 had been carried out. It related to static and not personal sampling.

123 It should be noted that in this report there is a good deal of variation demonstrated between the three readers of the chest radiographs. It should also be noted that in the absence of controls several assumptions have had to be made with regard to the physiological data. It does not appear from this report that there is any clear order of appearance of adverse effects in relation to asbestos exposure.

124 Overall, it is reasonable to conclude from these data that, with the improved hygiene standards now implemented, the occurrence of features that might reflect on adverse effect of asbestos on the lung (but which are also common in many other lung diseases) are likely to be found in only a very small number of workers after a lifetime of exposure.

Appendix D

Problems of measurement of dose and response

125 The difficulties of measurements in these two areas, and the interpretation of relationships between them, have been mentioned briefly in the body of this paper and were considered in more depth in our previous report (Acheson and Gardner, 1979a). A short summary is provided here.

Measurement of dose

126 Ideally the measurement required is the dose of fibre reaching the target organ and remaining there long enough to produce a deleterious effect. In man, however, the only information available, if any, consists of estimates of dust in the workplace available to be inhaled. Methods of measuring dust and fibres have changed with time, and reconciliation of measurements made with different techniques is far from straightforward (Steel, 1979). Instruments have changed with the membrane filter sampler replacing the thermal precipitator, fibre counting replacing particle counting, the 'eyepiece graticule' replacing the 'whole field' method of counting, and personal samplers attached to the workers replacing static samplers.

127 Two other relevant aspects are that some proportion of asbestos fibres taken into the body remain and may be active for prolonged periods, and that the disease may appear after exposure has ceased. These points can be taken account of when producing an index of dose by weighting the exposure by the estimated residence time within the body, by making various assumptions about the rate of decay of activity of fibres in the body (Berry *et al*, 1979), and by making allowances for cases of disease occurring after workers have left the factory.

Measurement of response

128 The comparison of observed mortality with that which would be expected on the basis of the death rates in an external standard population is the most common procedure for measuring response. This enables the study group to be assessed against a predominantly unexposed population for diseases of interest. The selection of an appropriate standard is often complex. Because of the extended time from first exposure to recognition of asbestos-related diseases a long period of follow-up is necessary to avoid misleading results. Appendix C has reviewed the problems in measuring morbidity.

Assessment of dose-response relationships

129 In using estimates of risk based on any of the available studies, the inadequacies and problems should always be borne in mind. The relationships between dose and response vary greatly in slope between the studies reported in Table 6. These differences may be due, among other reasons, to:

(a) exposures to different fibre types or mixtures;
(b) different work conditions;
(c) varying accuracies of dust measurements, arising from different methods and positions of dust sampling, techniques of counting, use of measurements from other locations or factories, and 'guesstimates' made where no measurement data are available;
(d) varying fibre: dust ratios;
(e) differences in size distribution of the fibres;
(f) different relationships between airborne fibre concentrations and the amount of fibre deposited in the lungs;
(g) differing follow-up periods;
(h) appropriateness or otherwise of external standard population;
(i) differences in background level of lung cancer in standard populations;
(j) smoking habits of industrial population relative to standard population;
(k) differences in smoking habits between men at varying levels of cumulative dose;
(l) use of retired population compared with a full cohort.

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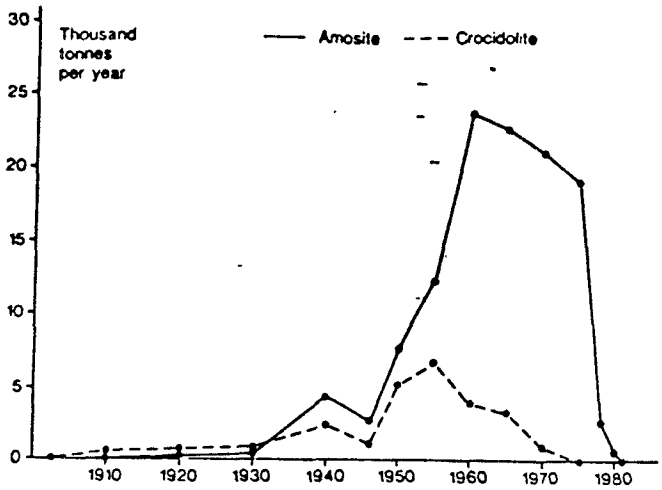
Figures

Fig 1 Trends in annual imports of amosite and crocidolite asbestos into the UK



Source Asbestos Information Centre Ltd

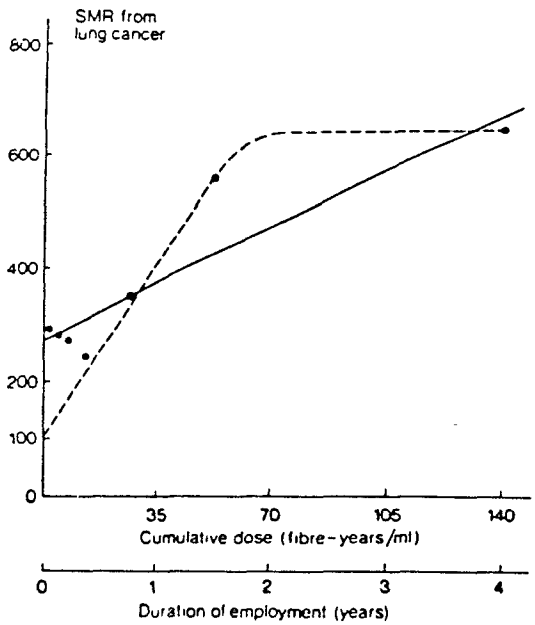


Fig 2 Mortality from lung cancer among amosite insulation production workers according to estimated cumulative dose of exposure to asbestos and duration of employment
... Individual data points from Seidman et al (1979)
--- dose-response relationship from Nicholson (1981)
— dose response relationship from Liddell (1982a)

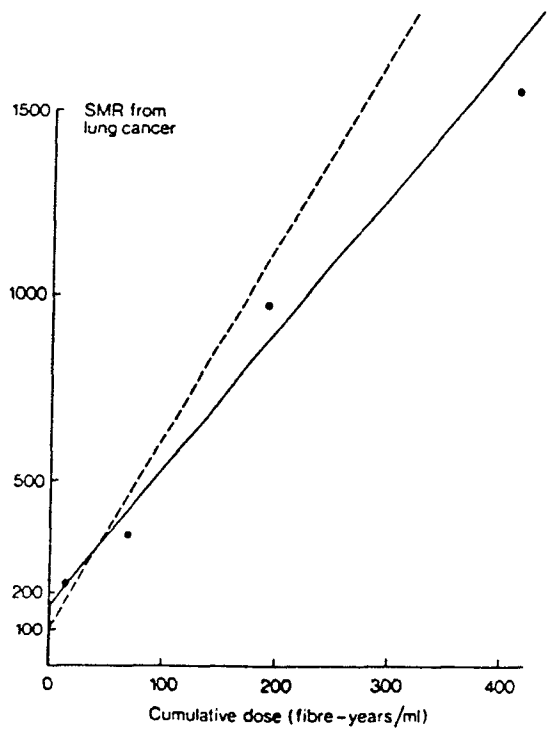


Fig 3 Mortality from lung cancer among chrysotile textile production workers according to estimated cumulative dose of exposure to asbestos
... Individual data points from Dement et al (1982)
--- dose-response relationship from Nicholson (1981)
— dose-response relationship due to Liddell from McDonald et al (unpublished a)

Tables

Table 1 Imports of raw asbestos fibres to the UK by amount (tonnes) and percentage of 1946 figure

	Chrysotile		*Crocidolite*		*Amosite*		*Total*	
Year	*tonnes*	*%*	*tonnes*	*%*	*tonnes*	*%*	*tonnes*	*%*
1946	50,700	100	1,000	100	2,700	100	54,400	100
1955	123,000	243	6,800	680	12,300	456	142,100	261
1965	147,000	290	3,400	340	22,600	837	173,100	318
1975	120,000	237	—	—	19,200	711	139,400	256
1978	123,000	243	—	—	2,700	100	125,800	231
1980*	89,500	177	—	—	700	26	90,200	166
1981*	76,400	151	—	—	261	10	76,700	141

*Figures for 1980 and 1981 are estimates. Amosite imports for 1982 estimated to be 16 tonnes.

Source The figures for 1946, 1955, 1965 and 1975 were given in Table 1 of our previous report. The figures for 1978, 1980, 1981 and 1982 have been provided by the Asbestos Information Centre Ltd

Table 2 Uses of chrysotile asbestos imported into the UK during 1981*

	Chrysotile asbestos	
Usage	*tonnes*	*percentage*
Asbestos cement	28,050	37
a) building products	26,350	35
b) pressure pipes	1,700	2
Friction materials	11,200	15
Floor tiles	8,000	10
Jointings & packings	7,250	9
Textiles	3,000	4
Other miscellaneous uses	18,900	25
Total	76,400	100

*These figures are estimates. In addition, 261 tonnes of amosite were imported and used in the manufacture of pressure pipes

Source Figures provided by the Asbestos Information Centre Ltd.

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		Number of mesotheliomas			Mesotheliomas	
					observed	excess[2]	pleural	peritoneal	total	% of all deaths	Ratio to excess lung cancer deaths
Men	*Mining and milling*										
	Chrysotile	McDonald *et al* (1980b)	9,810	3,291	230	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[3]	0	0
	Anthophyllite	Meurman *et al* (1974)	1,041	248	21	8.4	0	0	0	0	0
	Talc	Kleinfeld *et al* (1967b)	220	91	9	6.7	1	1	2	2.2	0.3
		Brown *et al* (1979)	382	74	8	5.2	7	7	1	1.4	0.2
	Crocidolite	Hobbs *et al* (1980)	4,960	181	38	5.4	16	0	16[3]	8.8	3.0
Men	*Manufacture*										
	Chrysotile	Thomas *et al* (1982)	1,540	351	24	−1.8	2	0	2	0.6	—
		Weiss (1977)	264	66	8	−0.6	0	0	0	0	—
		Dement *et al* (1982)	746	191	26	18.5	0	1	1	0.5	0.1
		McDonald *et al* (unpublished a)	2,543	570[4]	59[5]	29.4[5]	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	X	X	8	18.6	2.0
	Amosite	Seidman *et al* (1979)	820	528	83	60.2	7	7	14	2.7	0.2
		Acheson *et al* (1981)	4,882	431	57	27.9	4	1	5	1.2	0.2
	Mixed	Newhouse & Berry (1979)	2,887	545	103	59.8	13	33	46	8.4	0.8
		Newhouse *et al* (1982)	8,804	1,640	143	3.5	8	0	8	0.5	2.3
		Peto *et al* (1977)	796	293	49	26.1	9	0	9	3.1	0.3
		Henderson & Enterline (1979)	1,075	781	63	39.7	7	?	4	0.5	0.1
		Robinson *et al* (1979)	2,666	912	49	12.9	4	5	13[3]	1.4	1.0
		Hughes & Weill (1980)	5,645	601	49	−0.1	0	0	0[3]	0	—
		Mancuso & Coulter (1963)	1,266	175	15	9.5	0	4	4	2.3	0.4
		McDonald *et al* (unpublished b)	4,137	895[4]	53[5]	2.5[5]	10	4	14	1.6	5.6
Men	*Insulation*										
	Mixed	Kleinfeld *et al* (1967a)	152	46	10	8.6	2	2	4	8.7	0.5
		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	381.4	63	112	175	7.7	0.5
		Elmes & Simpson (1977)	162	122	35	30.0	8	5	13	10.7	0.4
		Newhouse & Berry (1979)	1,368	83	21	15.4	10	0	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	385	35	11.5	0	0	0[6]	0.8	0
Women	*Manufacture*										
	Chrysotile	McDonald & Fry (1982)	848	122	1	−1.5	0	0	0	0	—
		Acheson *et al* (1982)	570	177	6	1.2	1	0	1	0.6	0.8
	Crocidolite	Jones *et al* (1980)	578	166	12	8.2	13	4	17[7]	10.2	2.1
		McDonald & McDonald (1978)	83	13	0	−0.0	X	X	2	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)	783	200	27	23.8	13	8	21	10.5	0.9
		Newhouse *et al* (1982)	4,219	346	6	−5.3	2	0	2	0.6	—
		Robinson *et al* (1979)	544	128	14	12.1	1	1	4[8]	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 1981, 48 pleural and 4 peritoneal, personal communication
6 Site unknown for 4 mesotheliomas in men and 2 in women
7 Updated 1981, 14 pleural and 3 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

Table 4 Exposure of cases of pleural mesothelioma and matched controls to crocidolite and chrysotile in a factory manufacturing friction materials

(a) Crocidolite

	Exposure to crocidolite			
Subject	*No known exposure*	*Fringe exposure*	*Definite exposure*	*Total*
Case	1	1	8	10
Control	30	7	3	40

(b) Chrysotile

	Exposure to chrysotile		
Subject	*Under 5 fibres/ml*	*5 fibres/ml or higher*	*Total*
Case	1	9	10
Control	30	10	40

(c) Crocidolite (Cr) and Chrysotile (Ch)

	Exposure (Cr, Ch)†				
Subject	*N,<5*	*N,5+*	*E,<5*	*E,5+*	*Total*
Case	0*	1	1	8	10
Control	26	4	4	6	40

†Cr, N = No known exposure, E = Exposed (definite or fringe), Ch, <5 = <5 fibres/ml, 5+ = 5+ fibres/ml
*If fringe exposure to crocidolite is disregarded, the numbers become 1, 0, 1, 8 and 29, 1, 8, 2 respectively for cases and controls

Source Newhouse *et al* (1982)

Table 5 Criteria employed to define the occurrence of adverse effects in the BOHS Committee on Asbestos morbidity study

A	At least two readers agreed that there were two or more steps of change on the profusion scale for combined small opacities over the interval between films.
B	At least two readers agreed that a pleural abnormality was present on the later but not on the earlier film of a pair (where 'pleural abnormality' means at least one of pleural thickening, pleural calcification, or costophrenic angle obliteration).
C	Unusual* rate of change in FEV_1
D	Unusual* rate of change in FVC
E	Unusual* rate of change in GtF
F	Any one measurement of $FEV_1/FVC < 0.70$
G	Chest sounds which did not clear on coughing or on any subsequent examinations

*'Unusual' is defined as any value in the lower 20 percentile of the distribution after adjustment for initial level, age, height, weight and smoking habits. See paras 54 – 58 in BOHS (1983).

Source BOHS (1983)

Table 6 Estimates of the slopes of the linear relationships* between mortality from lung cancer and cumulative asbestos exposure in various studies of asbestos workers

Study number (for reference see text)	Types of asbestos	Estimate of slope by: Acheson and Gardner (1979a) (SMR)	Nicholson (1981) (Selikoff, 1981) (SMR)	Liddell (1982)	Original authors
1	Ch	0.06	0.06	0.038† (RR)	0.038 (RR)
2	Ch	—	0.15	0.045 (SMR)	0.15 (SMR)
7	Ch	—	5.3	1.6[a] (RR)	4.0[b] (SMR)
8	Ch	—	—	=1.6 (RR)	1.7+[c] (RR) 2.0+[d] (RR)
9	Ch, Cr	—	—	0.058 (RR)	0.058 (RR)
6 E	Ch, Cr	0.5	0.07	—[e]	0.5 (SMR)
6 L	Ch, Cr		0.8		
3	Ch	0.125	0.3	0.12 (RR)	0.219 (SMR)
5	Ch, Cr, A	0.42			
4	Ch	—	1.1	0.5 (SMR)	—
15	Ch, A	—	1.7	1.5 (SMR)	—
10	Ch, Cr, A	—	—	0.22 (RR)	—
13 M	Ch, Cr, A	—	1.3	0.4—1.1 (RR)	—
13 F	Ch, Cr, A	—	8.4	2.7 (RR)	—
11	Ch, Cr, A	—	—	—	1.7+ (RR)
14	A	—	9.1	1.1 (RR)	—

E = pre-1951 entry, L = post-1950 entry; M = males, F = females; Ch = Chrysotile, Cr = Crocidolite, A = Amosite.

† = Liddell F D K, Thomas D C, Gibbs G W and McDonald J C Fibre exposure and mortality from pneumoconiosis, respiratory and abdominal malignancies in chrysotile production in Quebec, 1926—75. In preparation.

a = Amended to 2.3 (Liddell F D K, personal communication).

b = Estimated from Fig 2 of Dement *et al* (1982).

c = From Fig 2 of McDonald *et al* (unpublished a), using as far as possible the same methods as Dement *et al* (1982) — incorporating an average conversion factor of 6, for million particles/cubic foot to fibres/ml, would give an estimated slope of 0.85.

d = From McDonald *et al* (unpublished b) using same methods as in study 11 — incorporating an average conversion factor of 6 would give an estimated slope of 1.0.

e = Liddell (1982) unable to make independent estimate.

\+ = Incorporating a conversion factor of 3 for million particles/cubic foot to fibres/ml into results of McDonald *et al* (unpublished a and b).

* = Either SMR = 100 + slope × cumulative dose in fibre-years/ml, for Standardised Mortality Ratio;

or $RR = 1 + \frac{\text{slope}}{100} \times$ cumulative dose in fibre-years/ml, for Relative Risk.

Table 7 Concentrations of chrysotile asbestos in fibres/ml to produce after 50 years' exposure stated excess proportions of deaths from lung cancer (as proportions of deaths from all causes) according to linear dose-response models at current male lung cancer rates in Britain

Study	Conversion factor+	Slope	Excess lung cancer mortality 0.5%	1%	2%
Miners and millers	3	0.04	2.5	5.0	10.0
Friction materials	3	0.06	1.7	3.3	6.7
Production Workers (E)	3	0.125	0.8	1.6	3.2
Textiles					
Rochdale (A)	—†	0.5	0.2	0.4	0.8
Rochdale (L)	—†	0.8	0.1	0.3	0.5
South Carolina (M)	3*	2.3	0.04	0.09	0.17
South Carolina (N)	3*	5.3	0.02	0.04	0.08
South Carolina (M)	6**	1.2	0.09	0.17	0.35
South Carolina (N)	6**	2.7	0.04	0.08	0.15

\+ = From millions of particles/cubic foot to fibres/ml

* = Except in the area where chrysotile was prepared for which a conversion figure of 8 was used (Dement *et al*, 1982)

** = McDonald *et al* (unpublished a)

E = Enterline (1981), A = Acheson and Gardner (1979a), L = post-150 entry cohort, N = Nicholson (1981), M = McDonald *et al* (unpublished a)

† = Conversion also made from million particles/cubic foot to fibres/ml at earlier stage of calculations

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From the Director of Hazardous Substances Division

Dr. Leonard Vance,
Director,
Health Standards Programs,
Occupational Safety and Health Administration,
200 Constitution Avenue,
Washington DC 20210,
U.S.A.

1 August, 1983.

Dear Dr. Vance,

I am pleased to say that the Acheson and Gardner report has now been published so there are now no restrictions on referring to it or quoting from it. The Health and Safety Commission were only able to give it preliminary consideration at their meeting on 19 July. It is therefore too early to say what view they will take about its conclusions and recommendations. They will be reviewing their policy on asbestos at their meeting on 23 August.

However, at their last meeting the Health and Safety Commission did decide that there should be a change in the recommended method for evaluating airborne concentrations of asbestos. The Health and Safety Executive will therefore be changing to the European Reference Method (i.e. the methods set out in the annex to the EC Workplace Directive on Asbestos) as soon as the necessary hardware has been obtained and retraining completed. Due to the time required to implement this change it is not likely to be formally introduced until 1984. The HSE Guidance Note will be amended accordingly in due course.

Yours sincerely,

p.p. C.D. BURGESS.

(dictated by Mr. Burgess and signed in his absence.)

DU 038427