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The burden of occupational cancer in Great Britain

Technical Annex 4: Mesothelioma

Prepared by **Imperial College London** and
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Technical Annex 4: Mesothelioma

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The aim of this project was to produce an updated estimate of the current burden of occupational cancer specifically for Great Britain. The primary measure of the burden of cancer used was the attributable fraction (AF), ie the proportion of cases that would not have occurred in the absence of exposure. Data on the risk of the disease due to the exposures of interest, taking into account confounding factors and overlapping exposures, were combined with data on the proportion of the target population exposed over the period in which relevant exposure occurred. Estimation was carried out for carcinogenic agents or exposure circumstances that were classified by the International Agency for Research on Cancer (IARC) as Group 1 or 2A carcinogens with strong or suggestive human evidence. Estimation was carried out for 2004 for mortality and 2003 for cancer incidence for cancer of the bladder, leukaemia, cancer of the lung, mesothelioma, non-melanoma skin cancer (NMSC), and sinonasal cancer.

The proportion of cancer deaths in 2004 attributable to occupation was estimated to be 8.0% in men and 1.5% in women with an overall estimate of 4.9% for men plus women. Estimated numbers of deaths attributable to occupation were 6,259 for men and 1,058 for women giving a total of 7,317. The total number of cancer registrations in 2003 attributable to occupational causes was 13,338 for men plus women. Asbestos contributed the largest numbers of deaths and registrations (mesothelioma and lung cancer), followed by mineral oils (mainly NMSC), solar radiation (NMSC), silica (lung cancer) and diesel engine exhaust (lung and bladder cancer). Large numbers of workers were potentially exposed to several carcinogenic agents over the risk exposure periods, particularly in the construction industry, as farmers or as other agricultural workers, and as workers in manufacture of machinery and other equipment, manufacture of wood products, land transport, metal working, painting, welding and textiles. There are several sources of uncertainty in the estimates, including exclusion of other potential carcinogenic agents, potentially inaccurate or approximate data and methodological issues. On balance, the estimates are likely to be a conservative estimate of the true risk. Future work will address estimation for the remaining cancers that have yet to be examined, together with development of methodology for predicting future estimates of the occupational cancers due to more recent exposures.

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CONTENTS

1. INCIDENCE AND TRENDS

The most comprehensive source of information on mesothelioma in Great Britain is the British Mesothelioma Register, set up in the late 1960s in response to reports associating the disease with asbestos exposure (McElvenny et al., 2005). Though only deaths rather than new cases are recorded, since mesothelioma is usually rapidly fatal following diagnosis, mortality information based on the register gives good indication of the disease incidence. The register also enables the assessment of year-on-year changes in mortality which would not be possible using national death data since mesothelioma was not separately identified in the International Classification of Diseases until revision 10. Details of how the register is compiled have been published previously (McElvenny et al., 2005).

The number of mesothelioma deaths each year has increased dramatically since the late 1960s. In 2004 there were 1969 mesothelioma deaths – more than 1% of all malignant cancer deaths in Great Britain – compared with 153 in 1968, the first full year for which data are available from the mesothelioma register. The majority of mesothelioma cases affect the pleura and a smaller number affect the peritoneum. However, the discontinuation in 1993 of medical enquiries to clarify the cause of death means that it is not possible to determine precisely the proportions affecting each site (McELvenny et al., 2005). Mesothelioma is much more common in males who typically account for about 85% of deaths each year. The long latency of the disease – typically 30-40 years – also means that most cases occur at older ages, with around two-thirds of cases occurring at ages 60-80 years. Deaths rates at ages below 55 have been decreasing since the mid 1990s while rates in older age groups are increasing, with the most rapid increases seen in the oldest age groups. This pattern is consistent with that expected as the peak in the number of annual deaths is approached.

The latest available projections of the future burden of mesothelioma in Britain – based on mortality from 1968-2001 – suggest that the annual number of deaths will peak somewhere between current levels and 2450 deaths in the year 2015 (Hodgson et al., 2005). The projections model suggests that for men in the highest risk birth cohorts – that is, those born in the late 1930s or early 1940s – mesothelioma may account for around 0.7% of all deaths in these cohorts. Though highly uncertain, long-range predictions suggest that around 65,000 mesothelioma deaths may occur over the next 50 years.

2. OVERVIEW OF AETIOLOGY

Inhalation of asbestos fibres has been recognised as the main cause of mesothelioma for many years. Analyses of the mesothelioma register by occupational group and geographical area support the conclusion that the continuing increase in mesothelioma mortality in Great Britain is largely a consequence of past asbestos exposures in occupational settings (McElvenny et al., 2005). These analyses show that occupations and geographical areas with the highest mesothelioma risks tend to be those clearly associated with heavy past asbestos exposures, for example, within industries such as shipbuilding, railway engineering, asbestos product manufacture, and construction. However, analyses of trends in risk over time are consistent with mortality due to specific high risk industries of the past levelling off, or falling, more recently as other sources of exposure have developed over a wider range of occupations and geographical areas. Workers with the highest risks today are likely to be those subject to incidental exposures during the course of their work, for example, building maintenance workers.

The focus of much of the epidemiological research carried out since the 1960s – when the association between mesothelioma and asbestos was first reported (Wagner et al., 1960) – has been on occupational exposures. However, non-occupational asbestos exposures, cases caused by other agents, and spontaneous cases may contribute to the overall burden to some extent. Several reviews of mesothelioma in relation to non-occupational asbestos have been produced which suggest that paraoccupational (or familial) asbestos exposures, neighbourhood asbestos exposures due to residential proximity to industrial sites where asbestos was used, and true environmental asbestos exposures due to naturally occurring deposits can present a risk of mesothelioma (Orenstein and Schenker, 2000; Gardner and Saracci, 1989; Ilgren and Wagner, 1991). However, there is uncertainty in the level of risk due to these exposure scenarios and some are less relevant to Great Britain – for example, naturally occurring deposits of asbestos tend to be found only in specific areas of the world, including parts of Turkey, Greece, Cyprus, New Caledonia, Corsica, and the USA. There is also evidence that other mineral fibres such as erionite can cause mesothelioma (Ilgren and Wagner, 1991), but again, exposure within Great Britain is unlikely. A further possible risk factor for mesothelioma is exposure to Simian Virus 40 (SV40), which was found to contaminate many Salk polio vaccines administered widely in the 1950s and early 1960s in developed countries – including Great Britain (Butel, 2000). However, although SV40 is capable of infecting and transforming cells from various species and has been detected in human mesothelioma tissue, one recent study casts some doubt on the validity of earlier studies (López-Ríos et al., 2004), and all human epidemiological studies to date have been inconclusive (Olin et al., 1998; Strickler et al., 1998; Fisher et al., 1999; Strickler et al., 2003; Engels et al., 2003). Finally, there is also some evidence that a small number of spontaneous mesothelioma cases occur each year in the absence of any exposure (McDonald and McDonald, 1994; Ilgren and Wagner 1991). Together with any cases caused by naturally occurring deposits of asbestos or other mineral fibres – though as mentioned these are unlikely in Great Britain – these form a background level of mesothelioma which can be though of as the number of cases that would have occurred in the absence of any industrial use of asbestos.

The potential causes of mesothelioma relevant to Great Britain have been summarised into three groups in Table 1 below. In order to estimate the contribution of mesothelioma to the overall burden of cancer due to occupation in Great Britain, the number of current cases due to occupational asbestos exposures (group 1) needs to be estimated. However, evidence from the literature about the groups 2 and 3 (in Table 1) will also help to inform the validity of this estimate.

Table 1: Potential causes of mesothelioma relevant to Great Britain

Group	Attributable cause
1	**Occupational asbestos exposures** Exposure during work activities – either due to an individual's own work, or due to the work of others in the same workplace.
2	**Paraoccupational and environmental exposures** Exposure outside work activities but resulting from the work activities of others, for example, laundering overalls used by asbestos workers Living close to industrial sites using or producing asbestos / asbestos products Living or working in buildings containing asbestos in poor condition DIY activities involving work with asbestos
3	**Background cases (cases that would have occurred in the absence of any industrial exploitation of asbestos)** Spontaneous cases occurring in the absence of any exposure Environmental exposures via naturally occurring asbestos or other mineral deposits (such exposures are unlikely to occur in Great Britain)

3. ATTRIBUTABLE FRACTION ESTIMATION

Calculation of attributable fractions for occupational exposures to carcinogens using data from epidemiological studies typically needs to take account of the fact that not all cases that were exposed to the carcinogen of interest will have been caused by it (Steenland and Armstrong, 2006). In other words, other sufficient causes for the disease may account for some of the exposed cases. However, mesothelioma at currently occurring levels in Britain has essentially only one cause i.e. asbestos exposure. In addition, although mesothelioma risk will depend on the totality of cumulative exposure across different settings, where occupational exposures have occurred, these are likely to account for most of the exposure accrued. Thus, one way of estimating the proportion of mesothelioma cases attributable to occupational asbestos exposure is to simply identify the number of cases with evidence of occupational asbestos exposure. However, the validity of this approach will depend on how judgements about occupational exposures are made. For example, if employment in certain occupations is used as a marker for occupational asbestos exposure, some of the cases among those classified as occupationally exposed on this basis will not actually be due to such exposures. Thus, the total number of cases in these occupations may be an overestimate of the AF due to occupational exposures. Conversely, Miettenen's formula (used for population-based studies) may lead to an underestimate of the AF since some genuine occupational cases may be missed if they arise from occupational groups not classified as exposed. A further concern relates to using AF estimates from studies based in other countries or those where cases are selected from particular regions within GB, since these studies may not be representative of the situation in GB.

The approach adopted in this report was, therefore, to make an informed judgement about the likely proportion of mesothelioma cases in Great Britain attributable to occupational asbestos exposures drawing on this evidence from previously published studies and in particular a recent, but as yet unpublished, population-based case-control study of mesothelioma in Great Britain.

Non-GB based studies

In a population-based case-control in the USA, the attributable risk of mesothelioma due to asbestos exposure was calculated using logistic regression to be 84.7% for males and 22.5% for females (Spirtas et al., 1994). Cases were classed as unexposed to asbestos if a number of conditions were satisfied: 1) the next-of-kin indicated at interview that the individual had never been exposed to asbestos; 2) the individual had never worked in one of nine jobs judged to be associated with asbestos exposure; 3) the likelihood of asbestos exposure was zero on the basis of a job-exposure matrix; 4) there were no cohabitors with asbestos exposure; 5) the individual was living more than two miles from an asbestos mine or mill. The authors thus attempted to exclude people with non-occupational exposures from the 'unexposed' category; this could have resulted in the study overestimating the proportion of mesotheliomas attributable to occupational exposures.

In a review of asbestos and cancer in Europe, Albin and coworkers cite three studies where assessment of asbestos exposure was based on presence of asbestos fibres in lung tissue analyses as well as on assessments of job histories (Albin et al., 1999). In the first study of 21 cases from the Helsinki area, 86% were identified as having at least possible occupational asbestos exposure. A second study of 131 cases from the Paris area, only 62% had an occupational history or lung tissue analysis indicative of asbestos exposure. However, in a third study of 85 mesothelioma cases from the Lund area in Sweden 84% had an occupational history or lung sample analysis result indicative of occupational asbestos exposure.

Using data from the French National Mesothelioma Surveillance Program the attributable risk of mesothelioma due to occupational asbestos exposure was recently estimated to be 83.2% for males and 38.4% for females (Goldberg et al., 2006). This programme includes 21 districts in France covering approximately one quarter of the total population, chosen to be representative of the France as a whole in terms of demographic, employment and economic activity characteristics, and it covers approximately one quarter of the French population.

GB-based studies

From a case series of 272 mesothelioma cases in the south east of England, 236 (86.8%) were judged to have definite or probable occupational asbestos exposure on the basis of an assessment by experienced occupational respiratory physicians of occupational histories constructed from a variety of sources (Yates et al., 1997). The authors conclude that the study may have overestimated the proportion attributable to asbestos exposure because of the way the cases were selected. The high proportion of male cases (93%) may also have led this being an overestimation of the overall attributable fraction.

In a mesothelioma case-control study in the Yorkshire region of England, 82% of the cases were classified as having likely or possible occupational exposure on the basis of occupational histories reported by next-of-kin at interview or from coroner's reports (Howel et al., 1997). Of the 185 cases in the analysis, 137 (74%) were male.

In a population-based case-control study of mesothelioma cases in Great Britain diagnosed during 2000-2005, 94% of male cases had worked in occupations likely to be associated with asbestos exposure, or had specifically reported substantial asbestos exposures – such as sawing amosite board. Application of Miettenen's formula suggested an AF for occupational exposures in males of 85%. (Julian Peto, personal communication). Only 35% of the female cases in this study had worked in occupations likely to be associated with asbestos exposure or had reported substantial exposures, and the equivalent AF for occupational exposures in females was 22%. There was evidence of an increased risk among men and women with paraoccupational exposure before age 30: 3% of men and 34% of women 'never employed' in occupations likely to be associated with asbestos exposure (and not reporting any substantial exposure) reported domestic exposure before age 30 (AF: 1.3% and 16% respectively for males and females).

Background mesotheliomas

Several lines of argument have indicated an annual background rate for spontaneous mesothelioma cases of around 1-2 per million, including levels of mesothelioma mortality in industrialised countries before 1950 and rates among children (McDonald et al., 1994). Assuming that the background rate is the same in both sexes, and that there is no difference in mesothelioma risk due to asbestos exposure between the sexes, the intercept of a straight line fitted on a plot of annual female deaths against annual male deaths may be used to estimate the background level. Applying this technique to the annual mortality data from the mesothelioma register for 1968-2004 suggests a background rate of around 1 per million per year in Great Britain, which is consistent with the rate suggested by McDonald and McDonald. A rate of 1 per million is equivalent to about 30 cases each year in males and the same in females – that is, about 60 background cases per year overall.

Summary

In the British studies considered here, between 82% and 94% of male mesothelioma cases were classed as occupationally exposed, and the recent mesothelioma case-control study by

Peto and co-workers (taken as being most representative of the situation in Great Britain) gave an AF for occupational asbestos exposure of 85% (95% CI: 82-88%). Collectively, these results suggest an estimate of the proportion of mesothelioma cases in males due to past occupational exposures of 85-90%, or about 1400-1500 deaths in 2004, is reasonable. If there are, in addition, around 30 background cases each year in males, this would suggest between about 150 and 250 male deaths remaining in 2004 due to past paraoccupational and environmental asbestos exposures.

The AF for occupational asbestos exposure in females based on the study by Peto and co-workers was 22% (95% CI: 14-30%). Combining the results of Peto and co-workers with those from two studies in which results were reported separately for females (Golberg et al., 2006 and Spirtas et al., 1994) gives an average AF of 29% (95% CI: 23-35%). Collectively (but informally assigning more weight to the results of Peto and co-workers as this is a GB-based study) these results suggest that a reasonable estimate would be that around 20-30% of female cases are due to past occupational exposures, or about 60-90 deaths in 2004. If there are also 30 background cases each year in females, this would suggest between about 180 and 210 deaths in 2004 due to past paraoccupational and environmental asbestos exposures, an estimate which shows some consistency with the result for males.

Table 2: Estimated attributable fractions and attributable numbers for mesothelioma deaths in Great Britain in 2004

Potential causes of mesothelioma	***Background***		***Paraoccupational /environmental***		***Occupational***		***2004 total***
	AF (%)	***Attributable Number***	***AF (%)***	***Attributabl e Number***	***AF (%)***	***Attributabl e Number***	
Men	2%	30	10-15%	150-250	85-90%	1400-1500	**1674**
Women	10%	30	60-70%	180-210	20-30%	60-90	**295**

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