The risk of mesothelioma and lung cancer due to asbestos exposure – an update including recent epidemiology

Mesothelioma incidence is continuing to increase in Britain with over 2000 deaths per year in men and 400 per year in women currently[1]. This is a consequence mainly of past occupational asbestos exposures (which peaked between 1950 and 1975 then fell sharply) and the long disease latency. Men born between 1935 and 1955 have the highest rates since they started work during the period of peak use. Annual mesothelioma deaths are expected to peak towards the end of this decade and then decline. The incidence of asbestos-related lung cancer is likely to be similar to mesothelioma.

Britain and Australia have the highest mesothelioma rates worldwide, followed by The Netherlands. Incidence here is more than twice as high as in the USA, Canada and all other Western European countries, and about 10 times higher than in Central or South American countries. Higher rates in Britain and Australia likely reflect the extensive use of amphibole asbestos, and amosite in particular[2].

A British mesothelioma case-control study showed that almost half of male mesotheliomas in men born typically in the 1940s were attributed to working in the construction industry with about a further quarter attributed to work in trades more traditionally thought of as high risk such as shipbuilding, lagging and asbestos product manufacture[2]. Former carpenters have particularly high lifetime risks of mesothelioma (6%) due to cutting asbestos insulation board (which often contained amosite) which was installed into many buildings for fire protection. A minority of female mesotheliomas (38%) were attributed to occupational or domestic exposures. The large remainder of unattributed cases implies that the lifetime mesothelioma risk among the general population who didn't work with asbestos, or live with someone who did, is about 0.08% for those born in the 1940s. This is substantially higher than for earlier generations and is presumably a consequence of the widespread opportunity for unwitting exposures among this cohort who lived through the period of peak asbestos use.

The UK imported several million tonnes of asbestos, including over half a million tonnes of amosite[3]. By 1980, crocidolite and amosite use had ceased in the UK, and chrysotile use had fallen by 90%, but a large amount of asbestos remains in many older buildings, and there is ongoing concern about the potential for environmental exposure to building occupants and occupational exposure during maintenance, renovation and demolition. It would therefore be useful to be able to predict mesothelioma and asbestos-related lung cancer risks for current-day asbestos exposure scenarios.

The HSE facilitated Working Group on Action to Control Chemicals (WATCH committee) considered the question of exposure-response relationships for low-level asbestos exposure in some detail starting in 2008, focusing on mesothelioma and asbestos-related lung cancer risk[4]. It considered the available risk models derived from epidemiological studies of asbestos-exposed cohorts and the uncertainties and unresolved issues in the epidemiology that affect the application of these models, particularly when extrapolating to lower exposures that are typically of interest today. The review focused on the meta-analysis by Hodgson and Darnton[5] which addressed the relatively small set of studies from the extensive epidemiological literature with sufficient information about exposures and the type of asbestos to permit the development of quantitative risk models, including key studies such as the Quebec chrysotile miners, the South Carolina textiles workers, the Australian crocidolite miners cohorts.

The available studies all suffer, at least to some extent, from a number of important limitations particularly with regard to the measurement and assessment of worker exposures, including: 1) a limited numbers of exposures measurements being available, 2) measurements tending to reflect the later time periods of particular exposure settings, 3) earlier measurements using particle rather than fibre counts, 4) considerable uncertainties in the conversion of particle to fibre counts, 5) use of area samples to estimate personal exposure measurements, 6) variation in fibre counting methods, and, 7) deficiencies in available work history information. Some studies also suffer from limitations in the diagnosis of mesothelioma and lung cancer and ascertainment of deaths.

In the light of these issues, Hodgson and Darnton considered that global assessments of mesothelioma and asbestos-related lung cancer set against the overall average cumulative asbestos exposures for each cohort arguably provides a better basis for estimating the risk per unit exposure than assessments based on within-cohort regressions which could be susceptible to bias to the null. Justification of the Hodgson and Darnton approach did nevertheless appeal to there being reasonably good agreement with internal regressions where available for specific cohorts. The meta-analysis showed that a simple categorization of the cohorts by asbestos fibre type explains much of the between study variation in the mesothelioma risk per unit of cumulative exposure: for the exposure conditions typical in the original studies (10 to 100 f/ml.yrs), populations exposed to crocidolite have about 500 times the risk, and populations exposed to amosite about 100 times the risk, of those exposed only to chrysotile, for at a given exposure. Populations with mixed exposure have risks in between those exposed to pure chrysotile and amphibole.

In contrast to the results for mesothelioma, fibre type alone does not appear to explain most of the variation in excess lung cancer risk between cohorts. Amphibole exposed cohorts do tend to have among the higher risks per unit of cumulative exposure, but the variation in the risk for mixed and chrysotile only exposed cohorts spans over two orders of magnitude. Workers exposed to chrysotile fibre in the South Carolina textiles cohort have a similar excess lung cancer risk to those exposed exclusively to amphiboles and about 100 times the excess lung cancer risk of those who mined the source material in Quebec. The possible reasons for this very substantial discrepancy have been debated at length in the literature and may include an overestimation of actual fibre exposures among the Quebec miners and there being a higher number of long fibres in the context of the textile operations in South Carolina. Although unrecorded amphibole exposure might explain the somewhat higher mesothelioma risk at South Carolina than Quebec, it does not seem to be a plausible explanation for the much higher lung cancer risk at South Carolina which is higher than that of mixed fibre cohorts that must have involved much higher quantities of amphibole. The South Carolina risk estimate is also about 10 times higher than that for the Rochdale textile cohort which used mainly chrysotile but also some crocidolite. Hodgson and Darnton effectively treated the South Carolina results as an outlier that probably only describe the chrysotile related risk in exceptional circumstances. Overall they considered the data to be suggestive of a 10 to 50-fold higher lung cancer risk per unit of exposure for amphibole vs chrysotile.

Initial assessment of mesothelioma risk per unit exposure by Hodgson and Darnton assumed a linear exposure-response within the range of exposures seen in the original studies. However, detailed comparisons of the numbers of pleural and peritoneal mesotheliomas showed that cohorts with higher amphibole exposures had a much higher proportion of peritoneal cases. This implies that at least one of these mesothelioma outcomes must have a

non-linear exposure-response. This motivated the development of a model with separate terms for pleural and peritoneal mesothelioma which, being non-linear, predicts a progressively higher risk than a simple linear exposure-response when moving down the exposure scale.

One important new study not included in the original meta-analysis was another cohort of textile workers who processed raw asbestos from Quebec[6]. Small quantities of amosite were recorded as being used at one of the four plants making up this cohort at which 3 of a total of 8 recorded mesotheliomas occurred. The mesothelioma risk estimate is similar to that based on the South Carolina cohort and about 10 times higher than the risk estimate for the Quebec miners, although amphibole exposure cannot be ruled out as – at least partly – explaining this higher risk[7]. The lung cancer results from the North Carolina study do not shed any further light on the discrepancy in the lung cancer risk between the Quebec and South Carolina cohorts: the internal cohort regressions give a risk estimate similar to the Quebec value whereas the estimate based on the global assessment of the overall excess lung cancer per unit of exposure is similar to the South Carolina risk value.

The WATCH committee concluded that the Hodgson and Darnton meta-analysis still gives a reasonable description of the mesothelioma and asbestos-related lung cancer risk which is consistent with the currently available epidemiology. However, they noted the many uncertainties in the data and that extrapolations of models to lower exposures, different (younger) starting ages and (longer) patterns of exposure should not be taken as reliable absolute risk values. They considered that extrapolated risk estimates might be most useful as rough indicators of the magnitude of risk to aid decisions in management of asbestos in different situations, and noted that there are risks arising from exposures below 0.1 f/ml.yrs – particularly for amphiboles[8].

Another meta-analysis by Berman and Crump based on largely the same set of studies fitted within cohort regressions for both mesothelioma and excess lung cancer in relation to cumulative asbestos exposure where there was sufficient data to do so[9]. These analyses assumed a linear exposure-response for both outcomes and provide sets of coefficients representing the potency of asbestos in causing mesothelioma and lung cancer in each cohort. Berman and Crump then developed separate meta-estimates of potency for mesothelioma and lung cancer in relation to amphibole and chrysotile exposure using a model in which they made adjustments for both the proportion of amphibole fibre and the size distribution of the fibres likely to be present in the exposures. They also took into account additional uncertainty in the epidemiological data due to various limitations of the original studies not captured by statistical confidence intervals alone. Using this approach their meta-estimates of potency reconciled much of the variation in the individual study potency estimates.

More recently, another meta-analysis of lung cancer in relation to asbestos exposure by Lenters et al. used a similar initial approach as Berman and Crump, but then applied quality criteria in a different way[10]. They observed that for five predefined quality criteria, the meta-estimate of the lung cancer exposure-response was always greater for studies meeting the criteria than those not. Furthermore, when excluding studies in a step-wise fashion not meeting each of the five criteria considered in turn, the meta-estimates appeared to increase monotonically at each step. This evidence of a positive correlation between study quality and the gradient of the exposure-response led to the conclusions: 1) that risk estimation should be based on a consideration of only the highest quality studies, and 2)

that due consideration of study quality casts doubt on there being a difference in potency of chrysotile and amphibole in the causation of lung cancer.

While in principle the consideration of study quality in this way seems useful, it is not clear that it is appropriate when applied to the relatively small number of available studies in this particular context. Only two studies meet all five quality criteria, one of which is the South Carolina study, the other which may be an outlier in the data set for other reasons. It is not clear whether these studies give the highest risk per unit exposure because, being of highest quality, they best describe some generally applicable relationship between asbestos exposure and lung cancer, or that they give high values because there is something particular about these studies that they are capturing. A more formal examination of the statistical issues involved in this work by Hodgson[11] suggests the two main findings of the meta-analysis are less robust than claimed and should be interpreted cautiously. For example, the observation of a monotonic increase in the meta-estimate is what would be expected given that the South Carolina study is a member of the final group of studies after excluding those of lower quality.

In the light of these considerable uncertainties, what can be done to assess whether the asbestos remaining in many UK buildings continues to pose a risk to today's workers and general building occupants? One approach based on lung fibre burden estimation is now beginning to show promising emerging findings. The asbestos lung content of tissue obtained from a random sample of younger pneumothorax patients will tend to reflect recent and current asbestos exposure conditions. Such lung burdens, characterised by Transmission Electron Microscopy, are being used to predict future mesothelioma risk in the general population and in specific occupations using the relationship between asbestos lung burden and mesothelioma observed in a recent UK-based case-control study. While these analyses cannot be used to estimate the lifetime risk for a specific individual who has been subject to a particular asbestos exposure, the initial results are already providing valuable data about the extent of the reduction in average asbestos exposures in successive birth cohorts. Further analyses aim to determine whether those currently working in construction and other occupations still have an elevated mesothelioma risk.

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