Estimation of the past and future burden of mortality from mesothelioma in France

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Abstract

***Objectives*—Firstly to evaluate future mortality from mesothelioma in France with an age-period-cohort approach and evaluate different hypotheses on risk of mesothelioma for the most recent birth cohort. Secondly to compare the results with a British and an American study. Thirdly to study if any trends were detectable on data for women which would be consistent with the consequences of increasing environmental exposure to asbestos.**

***Methods*—Estimates of mortality from mesothelioma among men and women in France from 1950 to 1995 were based on the analysis of the pleural cancer mortality data coded 163 in the ninth revision of the international classification of diseases (ICD-9). Correction factors were used to derive the mortality from mesothelioma from these data, based on two regional registries. The analysis of the past mortality data has been performed by an age-cohort model (with a maximum likelihood technique). Predictions of deaths from mesothelioma over the next 50 years were based on four different assumptions on the risk of death from mesothelioma in future birth cohorts.**

***Results*—The predicted lifetime probability of dying from mesothelioma increases until the last birth cohort 1964–8 among men whereas it decreases strongly from the 1954–8 birth cohort among women. The projected numbers of deaths from mesothelioma in France until 2020 are similar, whichever hypothesis is considered: around 20 000 deaths from mesothelioma might occur among men and 2900 among women from 1996 to 2020.**

***Conclusions*—French data show an increasing lifetime probability of death from mesothelioma in the more recent male cohorts. Although the mortality burden can be predicted untill 2020, and is intermediate between the United Kingdom and United States estimates, there is still high uncertainty on the figures after 2020. No increase is found in women, and this does not support the hypothesis that current environmental exposure to asbestos could be associated with a detectable risk of death. Specific surveillance should be set up to monitor future trends or their absence.**

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The increased risk of mortality from mesothelioma and lung cancer in people exposed to asbestos has long been recognised. The first studies which directly measured these risks were generally based on subjects working without any protection and heavily exposed to asbestos: this is, for example, the case for the epidemiological study conducted by Selikoff *et al* in 1979[1] on 17 800 workers in the insulation industry exposed during the 1950s, and similarly in France, for the study we conducted on workers in the asbestos cement industry.[2] These results founded the implementation of the first regulation about occupational limit exposure.

More recently, several studies[3–5] have indicated that the risk of mesothelioma and—to a lesser extent—of lung cancer was lower in subjects exposed to chrysotile than in subjects exposed to amphibole (one of the two categories of asbestos fibres). As a consequence of this epidemiological evidence, various measures of protection were taken by different countries, at different times, for the workers in the asbestos industry: limiting the threshold of exposure of workers to asbestos; banning all fibres but chrysotile; and banning all fibres. In France, the regulation began in 1977 (with a limit of 2 f/ml lowered to 1 f/ml in 1987 and 0.6 f/ml in 1992). After the directive 91/659 of the European Commission, the use of any fibre but chrysotile was effectively banned in 1993. However, due to the long period of latency of mesothelioma and lung cancer, the impact of such measures cannot yet be evaluated.

Moreover, these measures did not deal with two important situations. Firstly, end users of asbestos products can certainly experience uncontrolled high exposures, at least for short periods of time. Secondly, large populations, such as people living, studying, and working in buildings with sprayed asbestos could be environmentally exposed to low concentrations of asbestos, but for a long time. The possible risks associated to these situations are much discussed and raise the issue of the extrapolation of effects observed in high to low doses.[2]

In 1995, the continuing debate in France on this public health issue was reactivated by the paper by Peto *et al*[6] the results of which were given considerable publicity in the French press[7–9] where they were described as forecasting a British epidemic of mesothelioma, and as forecasting the huge price that the United Kingdom population was likely to pay in deaths related to asbestos, a price that the French were likely to pay as well. An expert committee, conducted under the auspices of INSERM (the

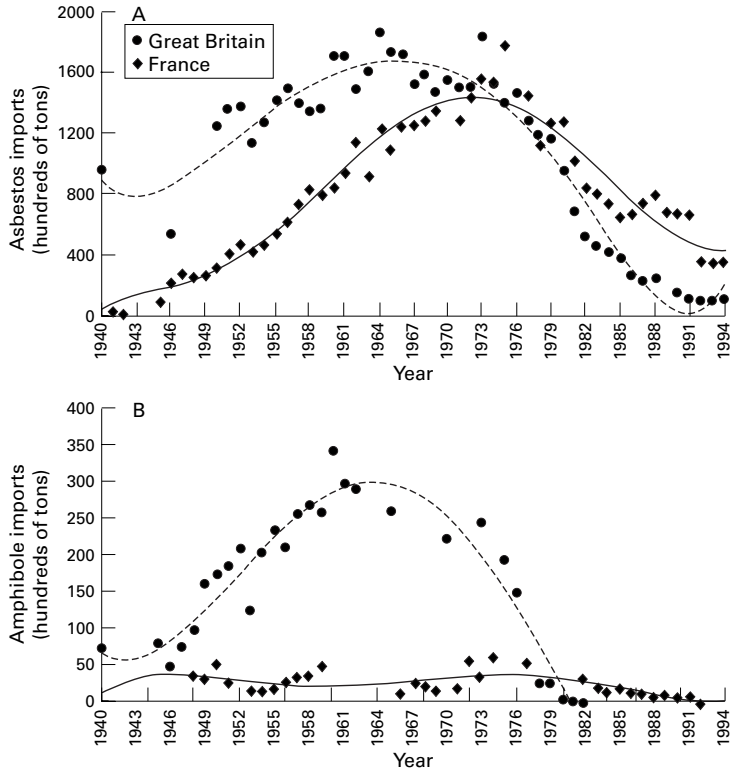

Figure 1 (A) Total asbestos imports, and (B) amphibole imports in France and the United Kingdom, 1940–94. Source: Association Française de l'Amiante. Curve fit is a sixth degree polynomial function.

French National Institute of Health and Medical Research), met in 1995 with the aim of evaluating the number of deaths attributable to asbestos and producing a review of the epidemiological evidence of the risk of asbestos, specially at low doses. Finally, the French government decided a complete ban of asbestos, effective from 1 January 1997.

The paper of Peto *et al* analysed the data of the British mesothelioma register, which is based on the analysis of the death certificates mentioning mesothelioma as a cause of death.[10] This study showed three results relevant to the estimate of the number of deaths from mesothelioma in the period 1968–2050: (*a*) the peak of the deaths from mesothelioma "epidemic" was expected in 2020, (*b*) the expected total size of the epidemic (from 1996 to 2020) was roughly 62 000 (this extrapolates to 166 per million inhabitants), (*c*) the lifetime probability of dying of mesothelioma is decreasing in the most recent generations compared with the older ones. In 1996, a paper by Price[11] used a comparable method to analyse the United States data of the surveillance, epidemiology, and end results (SEER) register. This paper broadened the analysis to the data on women, which were considered as giving an insight on the possible environmental risk of asbestos, as few women worked in the asbestos industry. Price found than the peak time of the United States mesothelioma epidemic was expected to occur in 1997, and that the expected total size of the mesothelioma epidemic (from 1996 to 2020) was 46 300—that is, 28 per million inhabitants. He did not find that the risk of death from mesothelioma in women was increasing.

This paper presents a similar study of the French data on mortality from mesothelioma. Our first objective was to study to what extent the future mortality from mesothelioma in France could be predicted, taking into account various possible hypothesis. Our second objective was to evaluate whether or not the difference of patterns in asbestos imports into France and the United Kingdom was associated with a difference in the mortality. Indeed, French imports have a larger proportion of chrysotile than British imports (fig 1), but the total imports were higher and later than in the United Kingdom. The third objective was to evaluate if any trend was found in women that could support a relation between environmental exposure to asbestos and mortality from mesothelioma.

Material and methods

ESTIMATING THE NUMBER OF DEATHS FROM MESOTHELIOMA

As there is no national register of mesothelioma in France, we estimated the mortality by mesothelioma in France as follows. Let: N=total number of mesothelioma death; N_{pl}=total number of pleural cancer death; $N_{pl,163}$=total number of pleural cancer death, coded 163; $N_{pl,oth.}$=total number of pleural cancer death, not coded 163; N_{ep}=total number of deaths from extrapleural mesothelioma (peritoneal and other sites than pleura); D_{163}=total number of deaths from pleural cancer coded 163.

A first study[12] conducted between 1 January 1987 and 31 December 1991 enabled us to estimate the number of pleural mesotheliomas (N_{pl}) as a function of the deaths coded 163 in ninth revision of the international classification of diseases (ICD-9) (D_{163}). In two of the 22 French regions (Ile de France and Provence Alpes Côte d'Azur-Corse) 178 deaths were confirmed as pleural mesothelioma by the National College of Anatomopathologists. The death certificates were found for all of these cases and 75% of the men were coded 163 as the principal cause of death ($N_{pl,163}$) and 70% of the women. From this we estimated that $N_{pl,163}/N_{pl}$ was 0.75 among men and 0.70 among women. A second study conducted from 1 July 1992 to 30 June 1993 in the same regions searched for all death certificates with a mention of code 163. One hundred and thirty

Table 1 Hypothesis on birth cohort risk of death from mesothelioma considered to realise prediction of death from mesothelioma 1996–2050

H1	Optimistic	The future birth cohort factors will decrease continuously to 0 (for cohort 2034–8), starting at the value estimated for the 1954–58 birth cohort
H2	Peto	The future birth cohort factors (after 1953) will be half of the factor estimates of the 1944–8 birth cohort
H3	Peto delayed	The future birth cohort factors will be half of the factor estimates of the 1964–8 birth cohort
H4	Pessimistic	The future birth cohort factors will stay at the level of the highest estimated past cohort factor

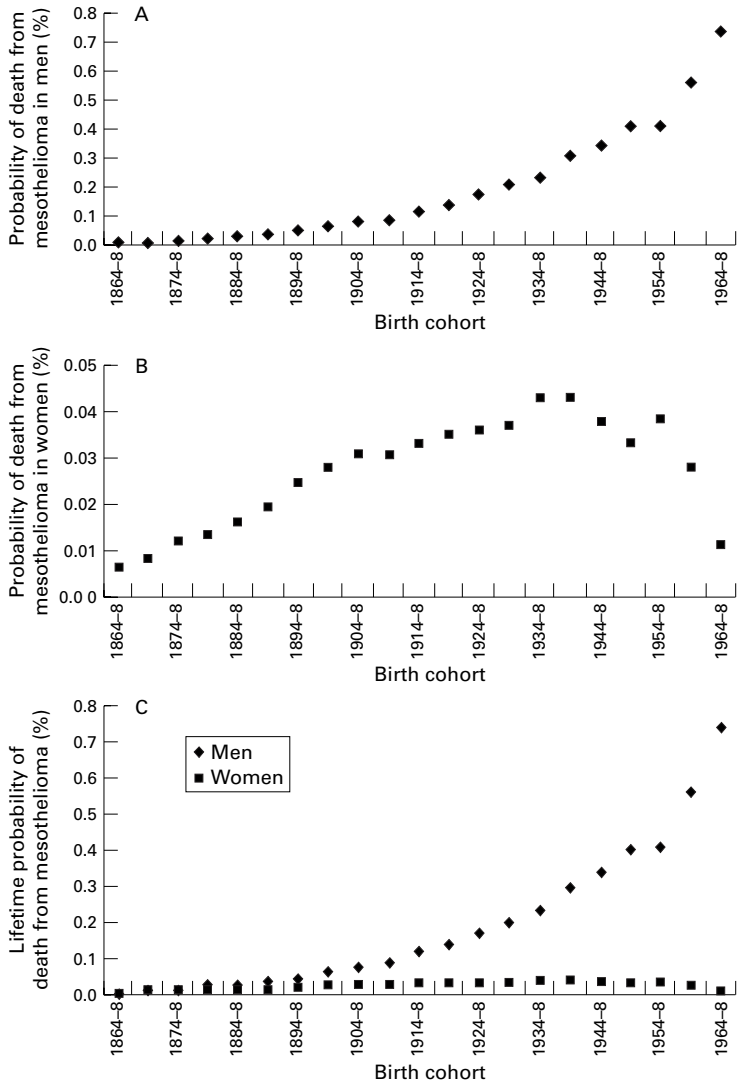

Figure 2 Lifetime probability (%) of death from mesothelioma 1864–8 birth cohort to 1964–8 birth cohort among (A) men, (B) women, and (C) both.

three cases were found, and among them 55% were found to be pleural mesothelioma among men and 25% among women. From this, we estimated that $N_{pl,163}/D_{163}$ was 0.55 for men and 0.25 for women. We deduced that N_{pl}/D_{163} was 0.73 for men and 0.26 for women.

In a third study,[13] the French collaborative network of cancer registries (FRANCIM, which covers 9.5% of the French population) was examined in 1992 and provided an estimate of the ratio N_{ep}/N of the total number of extrapleural deaths from mesothelioma (N_{ep}) and the total number of deaths from mesothelioma (N): 8% for men and 26% for women. Thus: N_{ep}/N was 0.08 (or N_{pl}/N was 0.92) for men and 0.26 (or N_{pl}/N was 0.74) for women.

Finally, these results can be used to derive an estimate of N (the total number of deaths from mesothelioma) from D_{163} (the total number of deaths from pleural cancer coded 163):

$N = D_{163}*0.55/(0.75*0,92) = 0.797 * D_{163}$ for men

and $N = D_{163} *0.25/(0.70*0,74) = 0.483 * D_{163}$ for women.

DATA

In France, the death certificate registries are under the jurisdiction of the INSERM. The database was used for the period 1979–95 with the ICD-9. For the years before 1979, deaths were coded with the previous revisions of the ICD and we used the French National Demographic Institute (INED) database which provides data standardised on the ICD-9 for the period between 1950 to 1978. This standardisation was made for all causes of deaths, sequentially, from ICD-3 to ICD-9, and the techniques used are described in detail in Vallin and Meslé.[14] We have extracted data on mortality from pleural cancer from these two databases. Data were available for men and women (separately) by the age at death in 5-year intervals from 25 to 89, and by year of death. From these two way tables, we reconstructed mortality by birth cohort (from 1864–8 to 1964–8) and age at death.

MODEL

Principle

We used an age-cohort model to predict the number of future deaths from mesothelioma.[15] In the model, effects on the probability of death of both age and cohort are separated. It is therefore possible to take into account the fact that a man of 80 (age), born in 1900 (birth cohort), will experience a lower mortality from mesothelioma than a man born in 1950, because he belongs to a cohort which was less exposed. Using a similar method to Peto *et al*[6] and Price,[11] the steps of our analysis were:

- Selecting an age-cohort model: we used a multiplicative model, assuming that all mortalities are the product of an age factor and a cohort factor
- Testing the model on the available data (1951–95)
- Making assumptions on the future cohort factors, for which we have no data.

Analysis of the past

Death rates for mesothelioma are presented by age group and by birth cohort—for example, mesothelioma death rate of age group 50–4 born in 1909–13 is 7.29 per 1 000 000. Those 117 mortalities are given for 13 groups of age and 21 birth cohorts. Let R(i,j) denote the observed death rate in age group i and birth cohort j—for example, R(6,10) is the death rate in the 6th age group (50–4) and the 10th birth cohort (1909–13)). Let A(i) be the effect of the ith age group and C(j) the effect of the jth birth cohort. All R(i,j) are a function of 13+21+1 unknown (13 age factors, 21 cohort factors, and 1 constant K), through the relation:

$R(i,j)=K*A(i)*C(j)$

Or, $R(i,j)=a_i*c_j$

where c_j is the risk of death from mesothelioma relative to a reference birth cohort and a_i is the age specific death rate in the age group i for this birth cohort. We arbitrarily chose 1864–8 as the reference cohort ($c_1=1$). Changing the reference—for example, $c_{10}=1$—would modify the a_i but would have no consequences for the final results.

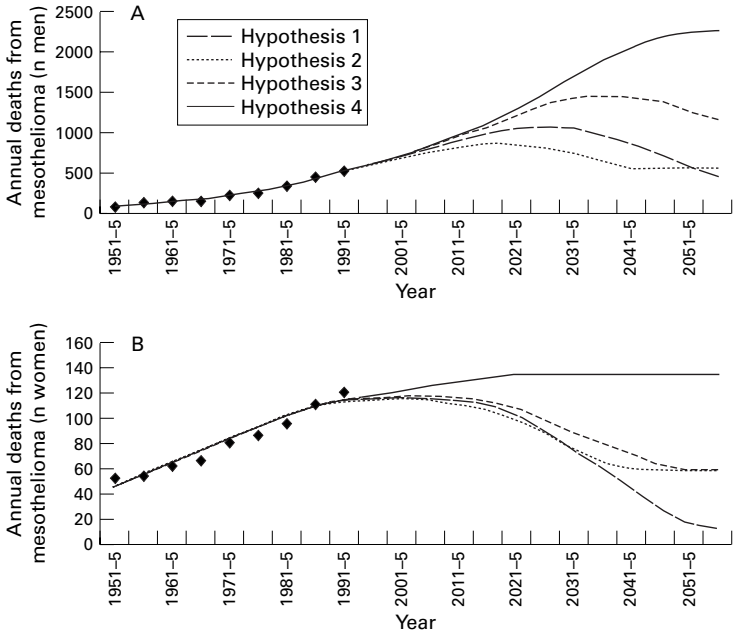

Figure 3 Predictions of numbers of deaths from mesothelioma in France among (A) men and (B) women, 25–89 years old at death, following the four hypotheses (H1 to H4) described in table 1.

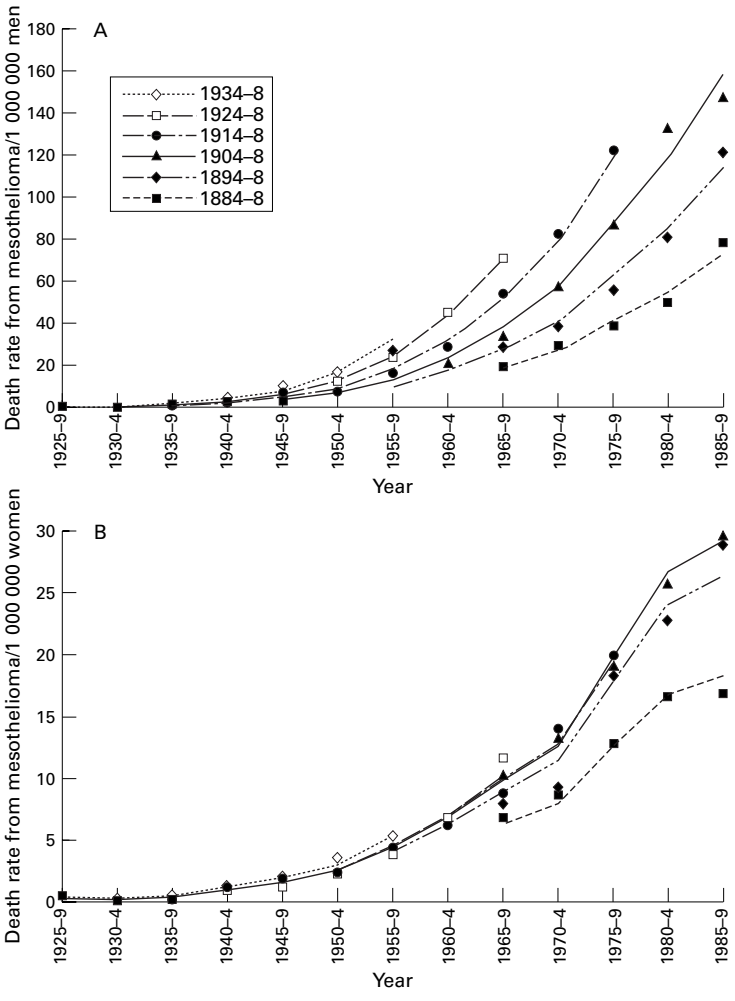

Figure 4 Age specific death rates from mesothelioma (/1 000 000) in France in several birth cohorts, among (A) men and (B) women, 25–89 years old at death from 1951–95. Dotted lines are data estimated from two French studies,[12 13] and continuous lines are data estimated from the age cohort model.

The components of the model are estimated jointly by the maximum likelihood method with a Poisson sampling assumption. GLIM[16] (generalised linear interactive modelling) software was used for these analyses.

The model estimates of the mortality of any age group i in a given cohort j are obtained by multiplying the line c_j factor by the column a_i factor. For example, the estimate of the mortality from mesothelioma of men aged 50–4 at death and born between 1909 and 1913 is 0.87×8.41=7.54 per 1 000 000. Also, c_j=8.41 means that the mortality of this generation is found to be (regardless of age) 8.41 times greater than the mortality of the reference value.

LIFETIME PROBABILITY OF DEATH FROM MESOTHELIOMA

Lifetime probability of mesothelioma death is computed by using actuarial methods. We collected data on mortality from causes other than mesothelioma, and French demographic data from 1950–95, for men and women separately (from INED and INSERM databases). After 1995 (of before 1950) we considered that the population has the same age structure and size as for the year 1995 (or 1950 respectively).

PROJECTIONS

From the 21 relative risks by cohort of mesothelioma death c_j and from the 13 age specific mortality ratios a_i estimated by the age cohort model, it is possible to reconstruct the mortality from mesothelioma among men and women born between 1864 and 1968 and dying between 25 and 89, with the relation:

$R(i,j)=a_i*c_j$.

However, estimates of our age-cohort model do not allow us to rebuild mortality from mesothelioma for all classes of age on a total after 1995—for example, on the 1996–2000 period, mortality is only rebuilt for 30–4 to 85–9 class of age, etc. Indeed, it would be required to know estimates of relative risks of death from mesothelioma of birth cohorts born after 1968. Because it is not possible with the available data, we have to hypothesise on the trend of this risk. We considered four different hypothesis (H1–H4), shown in table 1 which will be referred to as optimistic, Peto, Peto delayed, and pessimistic. Hypothesis H3 (Peto delayed) was considered because the timing of the asbestos imports (exposure) were roughly 10 to 15 years later in France than in the United Kingdom. The pessimistic hypothesis was considered because (unlike Peto *et al* and Price) we found that the latest cohort factors were not decreasing among men (see results section).

Results

Mortality from mesothelioma for men and women (aged 25–89) is presented in figure 4, in which the good fit between data and the age cohort model can be seen. The age specific mortality ratio increases clearly with birth cohort among men whereas this phenomenon is less apparent among women. Indeed, among men, for a given age (for example 75–9), mortality in a given birth cohort (for instance

Table 2 Estimate of annual number of deaths from mesothelioma among men per 10 000 000 inhabitants in France, United Kingdom[6] and United States[11] between 1996 and 2020

	Deaths from mesothelioma (n/10 000 000)	Peak	
		Year	Annual deaths (n)
France	430	2020–60	900–2200
Great Britain [6]	1660	2020	3300
United States [11]	280	1997	2300

1904–8) is always greater than the mortality of earlier cohorts (1894–8 and 1884–8), which is not the case for women. Age standardised mortalities (per 1 000 000) were computed, taking as reference the 1950 French population. It increases constantly from 5.81 to 25.75 between 1950 and 1995 among men (the total increase during this period is about 343%). Among women, two separate periods can be considered: from 1950 to 1981, it increases from 3.13 to 5.17 and then stabilises around 5. The total increase on the 1950–95 period is 75%.

Lifetime probability of death from mesothelioma is presented in figure 2. For men, the probability estimates increase continously from the 1864–8 to the 1964–8 birth cohort. However, this increase is not significant because the last two probabilities are very imprecise as they are estimated on very few points. The 95% confidence intervals (95% CIs) show this point: the mean (95% CI) value for the 1859–63 birth cohort is 0.56% (0.02% to 15.2%), and for the 1964–8 birth cohort the variability is greater, with an estimated 95% CI of 0.00075% to 0.514%. Among women, the probability increases more smoothly from the first cohort up to 0.043% for the cohort 1934–8 and then decreases to 0.01% for the last cohort.

Predictions have been realised for men and women separately according to these four assumptions and the annual numbers of deaths from mesothelioma are presented in figure 3. On all the hypotheses considered (H1 to H4), predictions are reasonably close until the year 2020. At this time, 1040 annual deaths might occur among men, 115 among women. The total number of deaths during the period 1996-2020 would be about 20 000 deaths among men and 2900 among women. After 2020, results for the different hypotheses are very different. The H4 predicts 2200 deaths from mesothelioma for men per year in year 2050 (135 for women) whereas H1 predicts <450 annual deaths for men (15 for women).

Discussion

The national mortality from mesothelioma was estimated indirectly from the pleural cancer mortality, 1950–95. As we had to do spatial and temporal extrapolations of regional studies performed at a single time of observation, caution should be exercised over several uncertainties. Our results show a constant increase in the age adjusted mortality from mesothelioma among men. By contrast with the results of Price and Peto *et al*,[6 11] this increase is not only due to the upward trend in the age class ⩾75. Indeed, the age specific mortalities indicate that all age groups contribute to this growth. This point is reinforced by our evaluation of the lifetime probability of mortality from mesothelioma. Although it decreases from the 1927 birth cohort in the United States and 1945 in the United Kingdom, it constantly increases in France until the last studied birth cohort (1964–8). However, estimates for the last two cohorts are computed from only four, six, and nine deaths on French, American, and British data respectively: uncertainty is large for all of these figures. With so few data, increases or decreases are not significant.

The trend of mortality from mesothelioma among women is very different. The age specific rates are roughly constant in age group 25–64 and increase strongly at older ages. Lifetime probability of death from mesothelioma indicates that the risk increases from the 1864–8 birth cohort to 1939–43 an then falls to 0.01% in 1964–8. It is much lower than among men, and in the same range as estimates given by Price (around 2.5×10^{-4}). As Price noticed on United States data, this result does not support increasing environmental exposure to asbestos. However, as it is well known that the development of a mesothelioma requires several decades (from 20 to 60 years) after the beginning of exposure, data analysed are the consequence of exposure before 1975, and recent changes in airborne asbestos cannot be evaluated.

The fit between observed data and estimates given by the age-cohort model is excellent, as shown in figure 4.

It is necessary to create a hypothesis to predict mortality from mesothelioma. We chose to consider four different hypotheses (H1 to H4) presented in table 1 from the most optimistic (H1) to the most pessimistic (H4). The choice of the hypothesis as a reduction of the lifetime probability of death from mesothelioma for the birth cohort after 1968 has little influence on the prediction until the year 2020 (see figure 3). Then, whatever hypothesis is considered, we can estimate that the annual number of deaths from mesothelioma might increase from 550 in 1996 to 1040 in 2020 among men and might remain constant at around 115 among women. After 2020, predictions vary strongly—depending on the hypothesis we consider—and we cannot determine which of these four hypothesis is the most realistic. Indeed, we do not know if the decrease in the lifetime probability among men will occur next year, in five years, in 10 years, or never. However, we are able to make a comparison between our results and those of Peto *et al* in Great Britain and Price in the United States, until the year 2020. The first difference is the pattern of the lifetime probability (already described) with different times of the peak of the epidemic (table 2). This should be reached in 1997 in the United States, in 2020 in Great Britain, and between 2020 and 2060 according to the hypotheses (H1 to H4) in France. These delays could, in part, be explained by the different patterns of asbestos consumption in these three countries. Indeed, American consumption began earlier (in 1880) than in Great

Britain and in France, and decreased, together with French imports, from the year 1975, whereas Great Britain reduced its imports before the mid-1960s. The second difference is in the size of the epidemic. The annual number of deaths predicted for the year of the peak is 3300 in Great Britain, 2300 in the United States, and varies from 900 (H2) to 2200 (H4) in France. The number of mesotheliomas per 10 000 000 inhabitants expected during the period 1996–2020 is much higher in Great Britain (1660) than in France (430) or in the United States (280). In other words, the expected number of deaths from mesothelioma per 10 000 000 inhabitants in France might be 1.5 times as large as in the United States and four times less than in Great Britain. These differences might, in part, be explained by different professional uses of asbestos or a different proportion of amphibole fibres in the asbestos, which is associated with the development of mesothelioma.[17–21] Indeed, we found the same difference between French and British amphibole imports, with a ratio of about 1:4.5. That could show a direct relation between amphibole imports and mortality from mesothelioma in both countries. The study of the relation between total asbestos imports and mortality from mesothelioma shows that there are other important factors involved, as total asbestos imports were only 15% lower than those in Great Britain (fig 1).

Conclusions

This study assesses the mortality burden associated with asbestos in France. Although it has to be acknowledged that many hypotheses, consistent with the available data, have to be considered, this work shows that it is possible to make a reliable prediction of the future deaths from mesothelioma up to the year 2020. The likely figures are 20 000 deaths in men from 1996 to 2020, which extrapolates to 43 deaths per million, which is lower than the corresponding British estimates and greater than United States estimates. A possible explanation can be found in the different fibres used in this country; France used a much smaller proportion of amphiboles than Great Britain. By contrast with the results found by Peto *et al* with British data, we found that our estimates of the lifetime probability of dying from mesothelioma were still increasing for men (although not significantly) in recent generations. This can certainly be explained by the French pattern of exposures which was delayed by comparison with the British one. More reassuring is the absence of trend that we found in the mortality from mesothelioma in women as Price found with United States data: this does not support the hypothesis that environmental exposure to asbestos plays an important part in mortality.

The analysis of mortality data is the only way to objectively describe the present trends in mortality from mesothelioma. However, it is clear that more precise results would require national mesothelioma registries based on representative samples, with quality assurance techniques providing confidence in the cancer and exposure data in the general population, and among the end users.

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