Bladder tumours in rubber workers: a factory study 1946–1995

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Background
Prior to December 1949, some British rubber industry workers were inadvertently exposed to the human bladder carcinogen beta-naphthylamine, which was present as a contaminant (at 0.25%) in antioxidants used in manufacturing. This study follows a composite cohort of 6450 men employed at a large tyre factory either during the 'at-risk' period or just after it.

Methods
A group of 2090 at-risk men (employed 1945–1949) and 3038 men, first employed only after January 1950, when the carcinogen had been removed, were followed for their bladder cancer morbidity and mortality experiences.

Results
Fifty-eight tumours were registered for those at risk, whereas only 33.9 were expected at national standardized registration rates [SRRN = 171 and 95% confidence interval (CI) = 130–221]. Thirty-nine bladder tumours were reported for the post-1950 intake, whereas 38.3 were expected (SRRN = 102 and 95% CI = 72–139). The use of mortality data did not reveal any underlying hazard because 12 of the 58 at-risk workers with tumours were still alive at the study end date. In only 16 instances was bladder cancer actually certified as the underlying cause of death. Plotting cases by their location of work on a factory plan assisted the interpretation.

Conclusions
A statistically significant elevated risk of bladder cancer for the exposed workforce was evident, but this reversed when the carcinogen was removed from processing in October 1949. The use of morbidity (incidence) data in long-term studies of occupational bladder cancer should be the required methodology if the hazard and risk are not to be underestimated.

Key words
Bladder cancer morbidity and mortality; carcinogens; rubber workers.

Introduction
The hazard of occupationally induced urothelial tract cancer in the UK rubber industry was forewarned by Case and Hosker [1] in 1954 but, at that time, the level of risk was undetermined. After several inquests a decade later, reminding everyone that the risk persisted, mortality studies were undertaken by both the British Rubber Manufacturers’ Association [2–4] and by the Health & Safety Executive [5], as well as in some factories [6]. This culminated in a common law test case for attributing liability and awarding compensation [Wright and Cassidy v. Dunlop Rubber Company Limited and Imperial Chemical Industries Limited (1971) QB]. Veys [7,8] gave a detailed bibliography, as did the World Health Organization/International Agency for Research on Cancer in their monograph devoted to the rubber industry [9].

An in-depth study was also initiated in 1964 at one of the 13 factories taking part in the British Rubber Manufacturers’ Association study in an attempt to define more precisely at shop floor level the extent of the hazard and risk to rubber workers employed between 1946 and 1949 when inadvertently exposed to the small quantities...
of beta-naphthylamine present in some of the antioxidants used. At the factory studied this potent human bladder carcinogen had been present as a contaminant in two antioxidants (Nonox S and Agerite Resin at ~0.25% or 2500 ppm) in continuous use between January 1934 and October 1949, when they were promptly withdrawn after a warning letter received from the manufacturers. During this period over 28,500 kg of Agerite Resin and 123,000 kg of Nonox S were compounded in processing.

Variously updated since 1969 [6–8,10], this report completes the final follow-up of the ‘at-risk’ group to December 1995. It also contrasts the bladder cancer experience, using both morbidity and mortality data, for all the pre-December 1949 employed workforce (some of whom were exposed to beta-naphthylamine, while others were not) with that of those workers only joining after January 1950, when the risk should theoretically have ceased after the withdrawal date in October 1949. In order to accommodate latency, it was important to ensure a sufficiently long follow-up of the post-1950 employed group to confirm that a reversal of risk had indeed taken place. In addition, some antioxidants still in use after 1950 were found to contain trace quantities (50–100 ppm) of beta-naphthylamine [10] and so final reassurance was also sought about these.

**Material and methods**

Essential personal details and exact work histories from complete company personnel records were computerized for a subsequent comparative composite cohort analysis using a specifically designed in-house programme of the Case and Lea analytical method [11]. This analysis uses an external reference in order to obtain standardized mortality ratios (SMRs) and standardized registration (incidence) ratios (SRRs) for comparing the expected numbers of deaths and cases of bladder cancer. These were calculated by applying sex, age, and the period-specific mortality and morbidity rates for England and Wales and for the Birmingham region (incidence only) to corresponding person-years at risk. Each study subject contributed person-years at risk only from the end of their quinquennial intake group, namely from 1951 for those employed up to December 1949 or from 1956 or 1961 for those employed between 1950 and 1960. Cases and deaths were included only up to age 85 years for the three reasons given by Sorahan and Nichols [12]. The 95% confidence intervals (CIs) were calculated using a microcomputer programme [13]. The reference data were taken from publications of the Office of Population Censuses and Surveys and from the World Health Organization/International Agency for Research on Cancer series of Cancer Incidence in Five Continents.

The composite cohort to be followed up was composed of two main groups. The first group numbered 3412 men who first joined between 1 January 1946 and 31 December 1949 or who had returned to regain their previous employment after the war years (1939–1945). This group was further subdivided into subsets of those considered to at any time have been at risk of exposure to the two beta-naphthylamine-contaminated antioxidants (2090) and those not at risk (1322). The second main group comprised 3083 men first employed only after January 1950, i.e. only when the purported carcinogens had been withdrawn from the manufacturing process. Theoretically, therefore, none of the post-1950 intakes would be considered to have been at risk. All cohort members had to have remained in continuous employment for 1 year in order to qualify for inclusion in the study.

An exact flow line of usage of the two requisite antioxidants was drawn up on a schematic factory plan, as shown in Figure 1. The two rubber mixes containing the antioxidants were traced by department and geographical location. These sites (at-risk areas) are shown on the plan by the shaded areas: from stores, to mixing and milling of rubber, to calendering and extrusion and on to the manufacture of miscellaneous items (hoses, membranes and conformation bags) and, finally, to the main inner tube manufacturing areas. The at-risk subsets also included all maintenance, work study, laboratory, supervisory and maintenance staff. Tyre mixings themselves were not involved, which fortunately greatly limited the number of men considered to have been exposed to risk.

Requisite ethical approvals were sought for the follow-up and tracing procedures. These were variously and periodically effected through the company personnel and pension records, through electoral registers, through the NHS Central Index at Southport, through the National Insurance Register at Newcastle-upon-Tyne, through former executive councils and later family health services authorities, through Medical Officers of Health records and, finally, through the Birmingham Regional Cancer Registry and Stoke Cancer Registry. Only 14 persons (0.2%) were not finally traced by the study end date of 31 December 1995. All deaths and any registrations for bladder cancer were selectively sought out and confirmed for the period 1951–1995, then set against the full nominal roll of the composite study cohort. Death certificate codings, as classified by the Office of Population Censuses and Surveys and the Registrar-General at Titchfield, were checked and generally accepted as recorded. Any coding queries were referred back to these authorities, usually by direct personal contact.

**Results**

The results showing the morbidity from bladder cancer in
the composite cohort of 6450 men who were employed between 1946 and 1949 are listed in Table 1. Between 1951 and 1995, 58 tumours were registered in the 2090 at-risk men, whereas only 33.9 were expected at national standardized registration rates (SRRN = 171 and 95% CI = 130–221). Expectation using the Birmingham Cancer Registry rates was a little higher: 35.8. The 1322 non-risk but concurrently employed workforce registered 18 tumours, whereas 21.1 were expected (SRRN = 85 and 95% CI = 51–135), with 22.6 expected at the Birmingham regional rates. A comparison of the standardized ratios between risk and all non-risk men gave a rate ratio (RR) of 1.8 (95% CI = 1.2–2.6). Discounting man-years not at risk and excluding those men engaged in 1950 only, the at-risk men were 2.8 times more likely to contract a bladder tumour than their non-exposed counterparts (95% CI = 1.8–4.4).

In contrast, the 3038 men first employed only after January 1950, when the risk had theoretically ceased after removal of the two contaminated antioxidants, registered 39 tumours with 38.3 expected using national rates (SRRN = 102 and 95% CI = 72–139). For regional Birmingham Cancer Registry rates the expectation was again a little higher: 40.2.

The single intake year of 1950, interposed between at-risk and non-risk times, was analysed separately. Any risk should theoretically have ceased in October 1949 and could be presumed to have been thoroughly clear after 1951. So the experience of the 461 men only engaged in that year (1950) was sought out in order to exclude any

Table 1. Morbidity from bladder cancer (1951–1995) in 6450 men employed between 1946 and 1960

<table>
<thead>
<tr>
<th>Category</th>
<th>Observed</th>
<th>EXPN</th>
<th>EXPB</th>
<th>SRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 2090 at-risk men employed 1946–1949</td>
<td>58</td>
<td>33.9</td>
<td>35.8</td>
<td>171</td>
<td>130–221</td>
</tr>
<tr>
<td>All 1322 non-risk men employed 1946–1949</td>
<td>18</td>
<td>21.1</td>
<td>22.6</td>
<td>85</td>
<td>51–135</td>
</tr>
<tr>
<td>All 3038 men first employed 1950–1960</td>
<td>39</td>
<td>38.3</td>
<td>40.2</td>
<td>102</td>
<td>72–139</td>
</tr>
<tr>
<td>Totals</td>
<td>115</td>
<td>93.3</td>
<td>98.6</td>
<td>123</td>
<td>102–148</td>
</tr>
</tbody>
</table>

EXPb, expected at Birmingham Cancer Registry rates; EXPN, expected at national registration rates; SRR, standardized registration ratio.

*Carcinogens discontinued in October 1949.
‘spill-over’ of risk. There were nine observed bladder cancer cases for the 1950 intake with 6.7 expected at national rates (SRRN = 134 and 95% CI = 61–255), but 7.3 expected at Birmingham regional rates.

In contrast, the analysis of mortality from bladder cancer using national data is shown in Table 2. With strict coding to the underlying cause of death under the International Classification of Diseases (ICD) classification system, 16 deaths due to bladder cancer (ICD 8–188) were observed, with 16.5 expected (SMRN = 97 and 95% CI = 55–157). Five certificates also mentioned bladder cancer but, because the tumour only appeared under part II or elsewhere, these deaths could not be coded to this cancer as the underlying cause. Five deaths from bladder cancer were observed for the 1322 non-risk men, with 9.8 expected at national rates (SMRN = 51 and 95% CI = 17–119). Nevertheless, four other certificates also mentioned bladder cancer. Some 15 deaths from bladder cancer were observed for the 3038 men first employed between 1950 and 1960 also not at risk, with 15.9 expected (SMRN = 94 and 95% CI = 53–156), but two other certificates also mentioned bladder cancer.

Table 3 summarizes the characteristics of all the cases (75) coming to light between 1946 and 1995 in any at-risk men. Twelve (21%) of the 58 cases of bladder cancer relevant to the at-risk men, who were exposed to the two beta-naphthylamine-contaminated antioxidants only between 1946 and 1949, were still alive at the study end date of 31 December 1995 and 46 (79%) had died. Of these latter, only 16 (27%) had died as a direct result of their bladder cancer with coding to ICD 8–188. Of the 30 who had died of other causes, 24 were without any mention of a urothelial tract cancer, whereas five did mention a bladder tumour in part II or elsewhere and there was one upper urothelial tract cancer of the renal pelvis.

Taken overall, searches revealed that some 75 cases of upper or lower urothelial tract cancer were finally located for any male employee who had ever been at risk at any time between 1934 and 1949. However, 17 cases were excluded from this analysis, either because of short (<1 year) service (10 cases) or because they had left before the study start date in 1946 (four cases) or because they had a singular pelvi-ureteric cancer in the upper urothelial tract (three cases). This left 58 cases relevant to the study analysis.

The mean exposure time of the 75 cases was 5.8 years, ranging from 1 month to 15 years 10 months. Fifteen men were exposed for less than 1 year, but most (33 cases) were exposed for between 1 and 5 years.

The mean age at diagnosis was 64.5 years, ranging from 43 to 87 years: eight men were in their forties and a further seven were younger than 53 years. An analysis of the age distribution indicated a higher proportion skewed to the younger ages (<55 years) than might have been expected if the distribution had accorded with the national norm over the same age groups and time span [14] (χ² for the trend = 15.19 and P < 0.001), but the numbers eligible for inclusion (73 under the age of 85 years) form only a small sample.

The mean latency period (first exposure to presentation) was 32.4 years for the 75 cases, ranging from 4 to 55 years: only three were less than 10 years, but 41 were between 20 and 30 years with five over 50 years.

<table>
<thead>
<tr>
<th>Table 2. Mortality from bladder cancer (1951–1995) in 6450 men employed between 1946 and 1960</th>
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<tbody>
<tr>
<td>Observed</td>
</tr>
<tr>
<td>All 2090 at-risk men employed 1946–1949</td>
</tr>
<tr>
<td>All 1322 non-risk men employed 1946–1949 a</td>
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<tr>
<td>All 3038 men first employed 1950–1960</td>
</tr>
<tr>
<td>Totals</td>
</tr>
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EXP N, expected at national death rates; SMR, standardized mortality ratio.

aCarcinogens discontinued in October 1949.

<table>
<thead>
<tr>
<th>Table 3. Characteristics of all the at-risk cases</th>
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<tbody>
<tr>
<td>• Seventy-five bladder tumours were recorded overall for men who had been at risk any time between 1934 and 1949: the mean latency was 32.4 years, the mean exposure time was 5.8 years and the mean age at diagnosis was 64.5 years</td>
</tr>
<tr>
<td>• Fifty-eight of these cases (77%) were relevant to the study analysis</td>
</tr>
<tr>
<td>• Twelve of the 58 (21%) were still alive at the study end date of 31 December 1995</td>
</tr>
<tr>
<td>• Forty-six of the 58 men (79%) in the study had died</td>
</tr>
<tr>
<td>• Twenty-nine had died of other causes, plus one of renal pelvic cancer</td>
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<tr>
<td>• Twenty-four of these death certificates made no mention of the bladder cancer</td>
</tr>
<tr>
<td>• Five mentioned the tumour in part II or elsewhere</td>
</tr>
<tr>
<td>• Only 22 only of the 46 deaths (48%) would be indicative of the underlying hazard and could contribute usefully to an analysis based only on mortality data, a loss of nearly half the data</td>
</tr>
</tbody>
</table>
Only five cases presented in at-risk female employees, but no formal enumeration or follow-up of women employees has been carried out because of name changes following marriage. Four of these women had worked on inner tube inspection in a fume-laden atmosphere.

There was also one case of carcinoma in situ in a male operative diagnosed in 1988. He eventually died of an unrelated cancer in 1994: the bladder dysplasia had not progressed in the intervening interval.

Figure 1 represents a schematic plan of the factory, with the relevant at-risk departments shaded, while non-risk areas remain white. The 58 bladder tumours in at-risk men employed before December 1949 are plotted individually on the plan as black squares with white circular insets, using their relevant employment at the at-risk time. It is of interest to note the preponderance of cases in the chemical stores and the mixing and mill room, i.e. the early stages in processing, where the risk of exposure to dust and fumes was greatest. In addition, many cases occurred in engineering fitters, who would go out on site into at-risk areas, often conducting their repair and maintenance work whilst production continued. The final risk to fitters of contracting a tumour was 3.7% and to mill men 4.6% of those who had ever worked in these areas. There were four ureteric/renal pelvic tumours (arrow-shaped plots with white circular insets) in at-risk men and only one in non-risk men. Such clustering of a relatively uncommon urothelial tract cancer is highly suggestive of an underlying occupational cancer hazard.

The clustering of five cases in the dispatch section is also noteworthy. Ordinarily, no risk would pertain for men handling the finished product for sale, essentially inner tubes. However, these men were sometimes called in to assist in the milling and mixing department when times were busy or labour was short. Thus, their at-risk situation was incidental to their normal work. The two cases in calendering (sheeting of rubber) marked on the edge of the department represent two men who worked on rubber cutting machines close to a calender on which mixes containing the carcinogenic antioxidants were handled. Other cases (four) were calender operatives.

In marked contrast, Figure 2 depicts the situation for those men only engaged after January 1950, when the risk had theoretically ceased. All these non-risk cases are plotted as black triangles. For easier comparison the shaded (pre-1949 at-risk) areas have been left in situ, because strictly speaking all areas were then non-risk and should be white. It is remarkable that the chemical stores, mixing and mill room, engineering, calendering and inner tubes are now largely devoid of cases compared to the pre-December 1949 exposure situation. The main tyre-making and curing workshops (located underneath

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**Figure 2.** Schematic factory plan showing urothelial tract tumours for men employed only after January 1950.
calendering and miscellaneous items on the plan), which are the largest departments, have changed little between both time periods. There are now no upper urothelial tract cancers recorded in the post-1950 employed men.

Discussion

This study set out to follow a large group of rubber workers, some of whom were exposed to betanaphthylamine contaminating two antioxidants used as compounding ingredients in processing up to the end of 1949, when they were promptly withdrawn. The advantages of a study at factory level are precise job definition and location, accurate assessment of an at-risk flow line, a clear-cut enumeration of the workforce involved and, in this case, improved case definition by using both morbidity and mortality data.

It was important to ascertain whether the risk was confined only to specific groups, who could then be advised about the need for follow-up cytology and to be able to reassure others that they were not at risk. It was of primary importance also to be able to reassure the workforce that the risk had ceased after 1950 when the suspect compounds had been withdrawn. This reassurance needed to be derived from a purposely conducted study and not just presumed, because several inquests on former rubber workers in the 1960s had caused alarm in both the general public and in the industry itself [15–17].

In essence, this study has confirmed that there was a significant excess risk for those operatives who had worked in areas (shaded on the maps) where it was deemed there was a risk of exposure to a proven human bladder carcinogen (see Figure 3). Risk was assessed using knowledge of the properties of the agent itself and the principles of occupational hygiene for exposure potential. Conversely, the study also showed that operatives deemed not to have been overtly exposed to the carcinogen did not experience any excess of bladder tumours, nor did those who were only employed after the discontinuance date. Reversal of a risk after taking ameliorating action provides strong evidence that there was indeed a hazard, where one had previously only been suspected [18]. Taken overall, the final total on the morbidity analysis with 115 tumours observed ($\text{SRR}_N = 123$ and 95% CI = 102–148) still hints at a hazard, despite the dilution afforded by the non-risk, post-1950 employed men (see Table 1), but not so with the analysis of mortality data (see Table 2), where there is under-representation ($\text{SMR}_N = 85$ and 95% CI = 60–118). The marked contrast in the number of cases available to the analysis, 115 on morbidity, but only 36 on mortality, is of some consequence. This study was one of ‘hypothesis testing’ with a clear definition of an at-risk situation. However, if the risk had not been foreseen and the same cohorts selected for follow-up in a ‘hypothesis-generating’ study using only mortality data based on the underlying cause of death, the hazard to the workers would have been missed (see Tables 2 and 3).

Apart from the statistical analysis, which is clear-cut (see Tables 1 and 2), useful confirmation was obtained by plotting individual cases on a factory plan. Mapping provides confirmation of location, clustering and reversal (compare Figures 1 and 2). The hazard and risk in dispatch workers only became apparent when an excess (cluster) of cases began to appear in a small group of workers handling the finished product and not normally considered to have been at risk, until it was noted that their work location changed when the occasion demanded it.

The presence of four much less common upper urothelial tract tumours plotted on the map in the at-risk group heralds a likely occupational hazard [19]. Additional pointers that assisted interpretation were that the risk was essentially confined to theoretically exposed groups and that there was a shift to younger ages at onset [19].

Overall, 75 cases of bladder cancer came to light in any operative who had ever been at risk, but only 58 were relevant to the population defined for study: 17 were excluded because of age, very short service, out of time or site (pelvis/ureteric). More disturbing in epidemiological terms was the potential loss of 42 cases from the analysis should this have been restricted to mortality data only, with coding to the underlying cause of death: 12 men were still alive at the study end date, the bladder cancer was not mentioned on 25 certificates and in five it was under part II or elsewhere. Thus, in only 16 cases (27%) was death due to bladder cancer certified as the underlying cause (ICD 8–188) and, thus, applicable to the analysis. Cancer incidence studies [20] have increased the potential for detecting excesses of cancer incidence in occupational groups, which may also be partly masked by the healthy worker effect [21].

Figure 3. An ‘at-risk’ rubber worker in the mixing department before 1950.
There was a small increased incidence of bladder tumours in the 461 men only engaged in the single year of 1950 itself (observed = 9, expected = 6.7, SRRN = 134 and 95% CI = 61–255), which might reflect a small spill-over of risk into that year, for it is difficult to concede that the risk ceased abruptly at the end of 1949 with the withdrawal date in October, taking into account possible use of residual stock, time for a change over of mixing formulae, factory cleaning and so on.

The under-representation of cases in the concurrently employed non-risk men (1322) working at the factory between 1946 and 1949 (observed = 18, expected = 21.2, SRRN = 85 and 95% CI = 51–135) may be due to some over selection into the at-risk group: sometimes the definition of an at-risk area was by a broad departmental boundary, in which the risk for some workers at the periphery may have been very slight or, realistically, nil. Likewise, in the at-risk group of 2090 men, some cases may have been missed because men did not return to the factory in 1946, even though they were exposed before the war, i.e. from 1934 to 1939, or had left before the study start date in 1946, having remained in their employment during some of the war years 1939–1945 or had then been called up for service in the forces.

Noticeably, the figures for expectation are all a little higher using the Birmingham Cancer Registry rates. This is to be expected because the Birmingham Cancer Registry covers an extensive conurbation, included in which are several large rubber factories and there are other occupational groups carrying a work-related hazard of bladder cancer; this would raise the rates.

Nevertheless, it is likely that most cases relevant to the analysis have come to light taking into account the length of follow-up (44 years) and the successful 99+% trace, together with the use of both national and regional cancer registries.

The mean latent interval was long (32 years), but this is a reflection of the time elapsing between any initial exposure potential from 1934 and the study end date in 1995: latency lengths on average as a study progresses over time and cases come to light. The mean exposure time was short (5.8 years) with 15 men exposed for <1 year and 33 men for between 1 and 5 years. Thus, despite the high dilution of this potent carcinogen in the original antioxidant used, short exposures seemed to offer little protection.

In 1969, Hueper [22] reviewed the question of an increased occurrence of multiple primary cancers in those workers previously exposed to benzidine and beta-naphthylamine. Other authors have reported likewise, suggesting a pluripotential action of these carcinogens [23–26]. Although there is some overall supporting epidemiological and animal experimental evidence, it is not sufficient to indent these agents as causing cancer elsewhere than in the urinary tract. In this study on rubber workers, there was a total of 14 second primary tumours in the 58 at-risk men, whereas only six were noted in the 57 non-risk men. Of the 14 second primary cancers there were four cases of lung cancer, two each of cancer of the rectum and oesophagus and one each of prostate, kidney, renal pelvis, stomach, colon and skin cancer. Thus, although in comparative terms an excess is apparent between the groups, small numbers preclude the firm conclusion of a statistically significant divergence from expectation (RR = 2.3 and 95% CI = 0.9–5.5).

Finally, as in many cohort studies that date back several decades from onset, adequate smoking histories were not available to the analysis, except in a few individual cases: notwithstanding that, men generally smoked more heavily in the war and in the post-war era. Nevertheless, the tobacco habit may in itself have provided a synergistic effect in the causation of some of the bladder tumours.

There were no occupational hygiene data available that related to the at-risk time of 1946–1949, so reliance had to be placed on knowledge of the process, the records of rubber mixings and use of the principles of exposure potential in occupational hygiene practice. Nevertheless, some readings taken in the 1970s confirmed the absence of beta-naphthylamine in the working environments. That the results came out correctly, i.e. the excesses occurred where it was deemed they should, is a reflection of the sound application of those principles.

In conclusion, this factory study, with long-term follow-up of a large cohort of rubber workers, some of whom were exposed to beta-naphthylamine-contaminated antioxidants used in processing, confirmed the presence and level of a past risk. This risk was confined only to those areas of processing in which there was the potential for exposure, but which ceased when the dangerous products were withdrawn in 1949. No risk remained for those first employed after 1951. Routine urine cytology continues on a six-monthly basis for rubber workers previously at risk from the beta-naphthylamine-contaminated antioxidants in use up to the end of 1949. There is a moral and legal obligation to do so. Realistically, however, the number of workers must be dwindling in relation to a hazard that theoretically ceased over 50 years ago. Despite selective screening, cases diagnosed now may only reflect the incidence in an ageing population and the residuum of a tobacco-related risk rather than an occupational one characterized by a very long latency.

Acknowledgements

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