Cancer mortality in the British rubber industry: 1946-80

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ABSTRACT The mortality experienced by a cohort of 36 445 rubber workers during 1946-80 has been investigated. These workers were all male operatives first employed in any one of the 13 participating factories in 1946-60; all had worked continuously in the industry for a minimum period of one year. Compared with the general population, statistically significant excesses relating to cancer mortality were found for cancer of the stomach ($E = 245.9$, $O = 282$, $SMR = 115$), primary cancer of the liver ($E = 12.8$, $O = 22$, $SMR = 172$), cancer of the lung ($E = 892.7$, $O = 1191$, $SMR = 133$), and all neoplasms ($E = 2165.2$, $O = 2487$, $SMR = 115$). Statistically significant deficits were found for cancer of the prostate ($E = 79.7$, $O = 59$, $SMR = 74$) and cancer of the testis ($E = 10.3$, $O = 4$, $SMR = 39$). The method of regression models in life tables (RMLT) was used to compare the duration of employment in the industry, the duration in "dust exposed" jobs, and the duration in "fume and/or solvent exposed" jobs of those dying from causes of interest with those of all matching survivors. Significant positive associations were found only for cancer of the stomach and cancer of the lung. The results of the RMLT analysis are independent of those from the SMR analysis, and the study has provided further evidence of a causal association between the risks of lung and stomach cancer and certain occupational exposures in the rubber industry.

In 1982 the Health Research Unit of the British Rubber Manufacturers' Association and the Cancer Epidemiology Research Unit of the University of Birmingham published a report describing the mortality experience of a large cohort of rubber workers in the United Kingdom.¹ The study found an "overall excess cancer mortality in the British rubber industry that is accounted for almost entirely by the observed excess of lung and stomach cancer." Apart from a small excess of oesophageal cancer, there was no evidence of any significant excess cancer mortality for other sites of cancer. The absence of any excess of bladder cancer affecting men who entered the industry after 1950 was noted.

An IARC working group also published an evaluation of carcinogenic risks in the rubber industry in the same year.² For lung cancer and stomach cancer, this report concluded that there was sufficient evidence for an excess occurrence in rubber workers and limited evidence for a causal association with occupational exposures.

This present study consolidates the data from earlier work, incorporates a further five year period of follow up, and reports more detailed analyses of relations between the risks of cancer mortality and job histories.

Study population

The study population (comprising three five year entry cohorts) has been described elsewhere¹ but may

Table 1 *Description of occupations*

Job No	Description
1	Crude material storeman
2	Compounding, weighing, mixing, reforming, washing, etc
3	Latex mixing, frothing, dipping
4	Extruding, calendering, spreading, etc
5	Component building, preparation, assembling, etc
6	Vulcanising, curing, moulding press, autoclave, pan
7	Inspection, painting, trimming, etc
8	Finished goods, stores, packaging, despatch
9	Site workers, internal transport, general truck drivers, etc
10	Engineering and building maintenance

be summarised as all male operatives first employed in any one of the 13 participating factories during 1946–60 inclusive, and who worked continuously in the industry for a minimum period of one year. Detailed job histories—defined in terms of 10 occupations or departments (table 1)—were recorded for each employee.

Follow up procedures have also been described elsewhere.¹ Before the present analysis was carried out, however, the vital status of each individual—as recorded in the computer file—was double checked with source data. Such data were held either by the National Health Service Central Register (NHSCR) at Southport, the General Register Office at Edinburgh, or the Health and Safety Executive. (The latter provided follow up information on men who featured in their own study of rubber workers.³) Company pension schemes are no longer generally being used for follow up, and workers formerly traced through such schemes are now “flagged” with the NHSCR at Southport.

Table 2 shows the vital status of the study population on the closing date of the survey. Only 3.7% were untraced. For those known to have died a death certificate was obtained with the underlying cause of death coded to the 8th revision of the ICD.

Table 2 *Vital status at closing date of study, 31 December 1980*

	No	%
Traced alive	24938	68.4
Emigrated	1228	3.4
No trace	1340	3.7
Deceased	8939*	24.5
Total	36445†	100.0

*Includes 75 deaths for which cause is unknown.

†Note 246 canteen workers listed in 1975 as “production workers” together with four duplicates have now been removed from the study.

Methods

The mortality experience of this cohort was compared with that which might have been expected to occur if rates of mortality for the general population of England and Wales or of Scotland had been operating on the study cohort, having due regard to the composition of the study cohort by age, sex, and calendar year.

Expectations based on person years at risk (pyr) were calculated using the Manyears computer program developed by J Peto. Individuals entered the pyr at the end of the first year of their employment and left on the date of death, date of embarkation, or the closing date of the study (31 December 1980), whichever was the earlier. Former employees who were

untraced left the pyr on the date last known alive. Individuals were “censored” on reaching their 85th birthday—thus no contributions were made to expected or observed numbers past this age. This was done for two reasons: firstly, national mortality rates are available only for the open ended age group ≥ 85 , and the composition of this age group in the general population by individual years of age may differ from that of the study population and, secondly, any individuals incorrectly traced as “flagged alive” (because their death was not recorded in the main index files at Southport or Edinburgh) would make a particularly large contribution to expectations for this age group.

This placed the mortality experience of the study cohort in broad perspective. The differences found between the observed mortality of an industrial cohort and an expected experience based on rates of mortality for the general population, however, clearly depend on factors other than specific occupational exposures.⁴ Such factors will include selection effects within the workforce as well as the regional and social composition of the study cohort. The method of regression models in life tables (RMLT) was used, therefore, to test the null hypothesis of no effect on mortality from occupational exposure in the rubber industry.^{5–7} Such exposures were here estimated crudely in terms of duration of employment in different occupations.

This method was used to compare the estimated occupational exposures of those who died in a given year of follow up with those of all matching survivors in the same year of follow up while controlling for year of starting employment (cohort 1, 1946–50; cohort 2, 1951–5; cohort 3, 1956–60), age at starting employment (15–, 20–, 25–, 30–, 45–, ≥ 55); industry sector (tyre, general rubber goods); and country of residence (England/Scotland). Follow up is measured from date of starting employment.

The data were first divided into a large number of subgroups by levels of the controlling variables mentioned above. For each subgroup (or subcohort) a life table was constructed, giving for each year of follow up the number entering that year of follow up, the number dying from the cause under investigation, and the mean cumulative exposure of these two categories.^{6,7}

The extent of occupational exposure was estimated in three ways:

- (1) cumulative duration of employment in the industry (irrespective of which departments were worked in);
- (2) cumulative duration of employment in jobs associated principally with dust (considered to be jobs 1, 2, and 4); and
- (3) cumulative duration of employment in jobs associated principally with fume or solvents or both

(considered to be jobs 4, 5, 6, and 7).

Of those who leave employment in any given year of follow up, a proportion will do so on the grounds of ill health. This group will, therefore, tend to be less healthy and, consequently, will have a higher rate of mortality than those remaining in employment. This effect is known as the “survivor population effect” and refers to a continuing selection process whereby the fittest remain or survive in the industry.⁸ For exposure estimates 2 and 3 it was possible to include “duration of employment in the rubber industry” as a controlling factor, to try and control for any survivor population effect in the data. Three levels of duration of employment in the rubber industry were considered (1–2, 3–7, ≥ 8 completed integer years). (A worker who was employed for 5 years 3 months would be placed in a “1–2” group for the first three years of follow up, and would be moved into a “3–7” group for all later years of follow up.)

The null hypothesis of no effect on mortality from the exposure is that the deaths in each year of follow up are a random sample from the entrants to that year and that the difference in the mean cumulative exposures of these two categories should be zero.

A test statistic was calculated to determine the probability of observing by chance alone the difference found between the exposures of those who have died and the exposures of the matching survivors—that is, if the null hypothesis is true. Since it is asymptotically normally distributed, a test statistic greater than 1.96 results in the rejection of the null hypothesis at the 5% level.

Several complementary analyses were also carried out in which two groups of workers were directly compared with each other with respect to mortality—for example, lung cancer mortality among tyre sector workers compared with general rubber goods workers, or stomach cancer mortality among those employed in jobs 1, 2, or 4 for at least 12 months compared with those never so employed. These analyses make use of the RMLT computer programmes, and the approach is equivalent to the log-rank

method used in the analysis of clinical trials.

The method was also used to estimate parameters of simple dose effect models—for example, latent period, doubling dose (exposure required to double the risk), and linearity of dose response. Latent period is not defined here as the interval between first exposure and death. Instead, exposure received in each year of employment is assumed to have a maximum effect L years later, where L is the optimum latent period. The procedures described above were repeated except that the cumulative exposure for each individual in each year of follow up was transformed into a relative risk predicted by the model under consideration. The risk of mortality predicted by the model for those who had died was compared with the risks of mortality predicted by the model for all matching survivors. A log likelihood was calculated to measure the goodness of fit of the specific dose effect model under consideration. The values of the parameters resulting in the highest likelihood were taken to be the “best” estimates of these parameters—maximum likelihood estimates (mle) (see appendix A).

Results

SMR APPROACH

The existence of any “healthy worker effect” in the data is best investigated by calculating SMRs for all causes for successive five year periods from first employment (irrespective of how long any individual remains in the industry).⁸ These are shown in table 3. There is a general trend of increasing SMRs over the follow up period, although the SMR for the last period is not consistent with this trend. Results are also given in table 3 for all cancers and for all non-cancers. There is little evidence of a healthy worker effect affecting cancer mortality.

Table 4 shows the overall results for cancer mortality by site. Compared with the general population, there are statistically significant excesses for cancer of the stomach, primary cancer of the liver, cancer of

Table 3 Mortality from all causes, all cancers, and all non-cancers by successive periods from first employment (irrespective of how long any individual remains in the industry): 1946–80

Years since first employed	All causes			All cancers (ICD8: 140–239)			All non-cancers		
	O	E	SMR	O	E	SMR	O	E	SMR
1–4	497	574.5	87	137	126.6	108	360	447.9	80
5–9	902	931.5	97	242	224.0	108	660	707.5	93
10–14	1329	1257.6	106	371	314.3	118	958	943.3	102
15–19	1807	1661.6	109	502	425.2	118	1305	1236.4	106
20–24	2012	1804.6	111	552	473.7	117	1460	1330.9	110
≥ 25	2311	2236.5	103	683	601.4	114	1628	1635.1	100
Total	8858	8466.3	105	2487	2165.2	115	6371	6301.1	101

Table 4 Cancer mortality for the total study population 1946-80

Site	ICD 8th	O	E	SMR
Lip†	140	1	1.0	100
Tongue†	141	7	7.0	100
Mouth†	143-5	7	5.8	121
Pharynx†	146-9	20	14.8	135
Oesophagus	150	73	58.8	124
Stomach	151	282*	245.9	115
Small intestine†	152	2	4.4	45
Large intestine†	153	124	130.3	95
Rectum	154	104	97.1	107
Liver†	155	22*	12.8	172
Gall bladder†	156	18	13.2	136
Pancreas	157	84	90.6	93
Nose, sinuses†	160	3	4.9	61
Larynx†	161	27	20.4	132
Lung	162, 3	1191***	892.7	133
Bone†	170	11	9.0	122
Skin†	172, 3	13	18.5	70
Breast†	174	2	2.8	71
Prostate	185	59(*)	79.7	74
Testis†	186	4(*)	10.3	39
Other genital†	187	3	3.3	91
Bladder	188	78	74.1	105
Other urinary†	189	36	37.3	97
Brain†	191, 2	51	59.0	86
Thyroid	193	8	4.0	200
Lympho	200, 202	38	40.8	93
Hodgkins†	201	16	24.3	66
Myeloma	203	14	19.6	71
Leukaemia	204-207	49	51.7	95
All neoplasms	140-239	2487***	2165.2	115

Two tailed tests throughout.

*p < 0.05; *** p < 0.001.

() Indicates significant deficit.

†Expectations were calculated on the basis of rates for England and Wales and rates for Scotland, except for those sites marked with a (†), for which rates for England and Wales only were used.

lung, and all neoplasms, and statistically significant deficits for cancers of the prostate and testis.

Table 5 shows observed and expected numbers of deaths by industry sector for seven causes of interest. SMRs are higher for the general rubber goods sector than for the tyre sector for all causes, all neoplasms, and cancers of the oesophagus, stomach, and lung.

The analyses shown in table 5 were repeated for each of the three entry cohorts. For the general rubber goods sector, a pattern of the highest SMR being found for the first entry cohort and the lowest SMR for the most recent entry cohort was found for all causes and for cancer of the lung. For the tyre sector, this pattern was not found for any of the seven causes

of death investigated, and for cancers of the oesophagus, stomach, and liver the highest SMRs were found among the most recent entry cohort.

Table 6 shows observed and expected numbers of deaths for five sites of cancer by successive periods from first employment (irrespective of how long any individual remains in the industry). No clear trends are shown. For cancer of the lung the highest SMR is found in the first period of follow up (within ten years from first employment).

Observed and expected numbers of deaths by first occupation were calculated for cancers of the oesophagus, stomach, liver, lung, and bladder. Compared with the general population, statistically

Table 5 Cause specific mortality by industry sector: 1946-80

Cause of death†	Tyre sector			General rubber goods sector		
Ca oesophagus	57	50.1	114	16*	8.7	184
Ca stomach	237*	208.4	114	45	37.6	120
Ca liver	20*	10.9	183	2	2.0	100
Ca lung	988***	757.6	130	203***	135.1	150
Ca bladder	69	62.7	110	9	11.4	79
All neoplasms	2082***	1838.7	113	405***	326.7	124
All causes	7731	7193.1	102	1527***	1273.2	120

†See table 4 for ICD categories.

*p < 0.05; *** p < 0.001.

Table 6 Cancer mortality 1946–80: SMRs (with observed numbers) by years from first employment. (Observed numbers of deaths on which the SMRs are based in parentheses)

Cause of death	Years from first employment			Total
	1–9	10–19	≥ 20	
Ca oesophagus	83 (6)	129 (24)	130 (43)	124 (73)
Ca stomach	105 (52)	146 (129)	93 (101)	115 (282)
Ca liver	95 (2)	195 (8)	179 (12)	172 (22)
Ca lung	150 (197)	126 (384)	123 (560)	133 (1191)
Ca bladder	101 (10)	122 (30)	96 (38)	105 (78)

significant excesses were found for the following: cancer of the stomach among those compounding, weighing, and mixing (occupation 2, Obs = 32, SMR = 152); cancer of the liver among those extruding and calendering (occup 4, O = 4, SMR = 364); and cancer of the lung among those compounding, weighing, and mixing (occup 2, O = 103, SMR = 134), engaged in component assembly (occup 5, O = 402, SMR = 138), inspectors and painters (occup 7, O = 46, SMR = 190), workers in finished goods (occup 8, O = 73, SMR = 145), site and transport workers (occup 9, O = 95, SMR = 154), and maintenance workers (occup 10, O = 211, SMR = 127).

REGRESSION MODELS AND LIFE TABLES

The method of regression models and life tables was used to investigate the possibility of an association between the risk of mortality for given sites of cancer (and other causes) and duration of employment in the rubber industry or duration of employment in particular departments.

Table 7 shows the overall test statistics, derived from comparing the duration of employment in the rubber industry of those dying from causes of interest with those of all matching survivors. Statistically significant negative test statistics are shown for all causes, all cancers, cancers of the oesophagus and lung, and non-malignant diseases of the respiratory system. The presence of a survivor population effect⁸ in the data will tend to produce negative statistics for these particular tests.

A significant positive test statistic is shown for cancer of the stomach. Non-significant positive statistics are shown for cancers of the bladder and liver.

The method readily allows an inspection of the contribution from subcohorts to the overall test statistic, and table 8 shows statistics for mortality from cancer of the stomach by levels of controlling variables. The significance of the overall test statistic can be seen to be dependent on the findings for deaths occurring among the first entry cohort, among workers in the tyre factories, and occurring after ten years

Table 7 Testing the null hypothesis of no effect from duration of employment in the rubber industry on risks of mortality by the method of RMLT.† (Test factor = cumulative duration of employment in the rubber industry)

Cause of death	ICD 8th	No of deaths	Mean exposure of deaths‡	Mean difference in exposure§	Test statistic
Ca buccal cavity	140–149	36	7.3	–1.6	–1.30
Ca oesophagus	150	73	7.2	–2.8	–3.04**
Ca stomach	151	282	9.9	+0.9	+2.19*
Ca liver	155	22	10.3	+0.7	+0.44
Ca digestive system	150–159	715	9.3	–0.1	–0.27
Ca larynx	161	27	8.6	–1.1	–0.76
Ca lung	162–63	1191	9.1	–0.4	–2.08*
Ca skin	172–73	13	8.3	–0.6	–0.32
Ca bladder	188	78	10.8	+1.0	+1.13
RES neoplasms	200–209	117	8.9	–0.5	–0.74
Leukaemia	204–207	49	8.6	–0.7	–0.69
All cancers	140–209	2468	9.2	–0.3	–2.01*
Diseases circulatory system	390–458	3933	9.4	–0.1	–1.10
Diseases respiratory system	460–519	1294	8.9	–0.4	–2.09*
All causes		8858	8.9	–0.4	–4.81***

*p < 0.05; **p < 0.01; ***p < 0.001 (two tailed tests).

†Controlling for age at hire (15–, 20–, 25–, 30–, 35–, 45–, ≥ 55), entry cohort, English/Scottish factories, general rubber goods/tyre sector.

‡In units of years of employment in the rubber industry.

§Mean difference in exposure between deaths and matching survivors in units of years of employment in the rubber industry.

||Asymptotically normally distributed.

Table 8 Testing the null hypothesis of no effect from duration of employment in the rubber industry on mortality from cancer of the stomach over levels of controlling variables by the method of RMLT.† (Test factor = cumulative duration of employment in the rubber industry)

Controlling variable	No of deaths	Mean difference in exposure§	Test statistic
By entry cohort:			
1946-50	169	+1.3	+2.16*
1951-55	67	+0.5	+0.68
1956-60	46	+0.1	+0.13
By industry sector:			
Tyre	237	+1.0	+2.26*
General rubber goods	45	+0.3	+0.27
By years of follow up:			
1-9	52	-0.2	-0.73
10-19	129	+0.6	+1.26
≥20	101	+1.8	+1.94
Total	282	+0.9	+2.19*

†, §, || See footnotes †, §, || for table 7.

*p < 0.05.

from first employment. These groupings are not mutually exclusive.

A similar tabulation was provided for mortality from cancer of the lung. All test statistics were negative. For cancer of the bladder, a positive statistic (1.32) was found for deaths occurring among the first entry cohort, whereas a small negative statistic (-0.08) was found for deaths occurring among the two later entry cohorts combined.

"Exposure" was here estimated as overall duration of employment in the rubber industry. If a hazard were only operating in certain departments, however, such a test would "dilute" any effect. It was, therefore, important to test the null hypothesis of no effect

on cancer mortality from working in specific types of jobs.

Table 9 shows test statistics comparing the duration of employment in jobs principally associated with "dust" exposure of those who have died from causes of interest with those of all matching survivors. None of the statistics shown achieves significance, although the positive test statistic for cancer of the stomach approaches statistical significance. Contributions from subcohorts to the overall test statistic for cancer of the stomach were obtained, and a significant statistic was found for deaths occurring among the first entry cohort ($t = +1.97$, $p < 0.05$). There is a negative test statistic for cancer of the lung.

Table 9 Testing the null hypothesis of no effect from duration of employment in dust exposure jobs on risks of mortality by the method of RMLT.* (Test factor = cumulative duration of employment in jobs 1, 2, or 4)

Cause of death	ICD 8th	No of deaths	Mean exposure of deaths†	Mean difference in exposure‡	Test statistic§
Ca buccal cavity	140-149	36	1.4	-0.1	-0.09
Ca oesophagus	150	73	0.8	-0.4	-0.86
Ca stomach	151	282	2.1	+0.4	+1.66
Ca liver	155	22	1.0	-0.6	-0.63
Ca digestive system	150-159	715	1.7	+0.1	+0.76
Ca larynx	161	27	2.1	+0.7	+0.94
Ca lung	162-63	1191	1.4	-0.2	-1.45
Ca skin	172-73	13	1.8	+0.8	+0.90
Ca bladder	188	78	2.1	+0.3	+0.60
RES neoplasms	200-209	117	1.2	-0.2	-0.57
Leukaemia	204-207	49	0.9	-0.5	-0.90
All cancers	140-209	2468	1.6	-0.1	-0.27
Diseases circulatory system	390-458	3933	1.7	+0.1	+0.80
Diseases respiratory system	460-519	1294	1.7	+0.1	+0.97
All causes		8858	1.6	+0.1	+0.77

*Controlling for age at hire (15-, 20-, 25-, 30-, 35-, 45-, ≥55), entry cohort, English/Scottish factories, general rubber goods/tyre sector, and duration of employment in the rubber industry (1-2, 3-7, ≥8 years).

†In units of years of employment in jobs 1, 2, or 4.

‡Mean difference in exposure between deaths and matching survivors in units of years of employment in jobs 1, 2, or 4.

§Asymptotically normally distributed.

Table 10 Testing the null hypothesis of no effect from duration of employment in fume and/or solvent exposure jobs on risks of mortality by the method of RMLT.† (Test factor = cumulative duration of employment in jobs 4, 5, 6, or 7)

Cause of death	ICD 8th	No of deaths	Mean exposure of deaths‡	Mean difference in exposure§	Test statistic
Ca buccal cavity	140–149	36	2.7	–1.2	–1.44
Ca oesophagus	150	73	3.9	+0.1	+0.16
Ca stomach	151	282	4.7	–0.2	–0.67
Ca liver	155	22	5.4	–0.2	–0.12
Ca digestive system	150–159	715	4.8	0.0	–0.09
Ca larynx	161	27	3.6	–0.8	–0.82
Ca lung	162–63	1191	5.0	+0.3	+1.65
Ca skin	172–73	13	5.1	+0.5	+0.35
Ca bladder	188	78	6.1	+0.8	+1.03
RES neoplasms	200–209	117	4.7	–0.1	–0.16
Leukaemia	204–207	49	4.3	–0.3	–0.42
All cancers	140–209	2468	4.3	–0.3	–0.38
Diseases circulatory system	390–458	3933	4.7	–0.2	–2.01*
Diseases respiratory system	460–519	1294	4.3	–0.3	–1.98*
All causes		8858	4.6	–0.1	–1.92

* $p < 0.05$.†Controlling for age at hire (15–, 20–, 25–, 30–, 35–, 45–, ≥ 55), entry cohort, English/Scottish factories, general rubber goods/tyre sector, and duration of employment in the rubber industry (1–2, 3–7, > 8 years).

‡In units of years of employment in jobs 4, 5, 6, or 7.

§Mean difference in exposure between deaths and matching survivors in units of years of employment in jobs 4, 5, 6, or 7.

||Asymptotically normally distributed.

Table 10 shows test statistics comparing the duration of employment in jobs principally associated with “fume and/or solvent” exposure of those who have died from causes of interest with those of all matching survivors. The test statistic for cancer of the lung approaches statistical significance ($p < 0.10$). Table 11 shows the contributions from subcohorts to the overall test statistic for cancer of the lung. The positive statistic for deaths occurring among the first entry cohort approaches statistical significance ($p < 0.10$). The positive statistic for deaths occurring among workers in the tyre sector is significant at the 1% level, whereas a negative test statistic is found for deaths among workers in the general rubber goods sector.

Several analyses were also carried out in which the mortality of one group of workers was compared directly with the mortality of another group of workers, using an internal rather than an external standard. For workers in the tyre sector, the risk of dying from lung cancer was 0.88 that of workers in the general rubber goods sector. This was not statistically significantly different from unity. A similar relative risk for all causes (0.86) was statistically significant at the 1% level. These risks are numerically similar to the ratios of the appropriate SMRs.

The risk of dying from lung or bladder cancer was higher among those employed in jobs 4, 5, 6, or 7 for at least 12 months compared with those never so employed, but these differences did not approach sta-

tistical significance (relative risks of 1.04 and 1.32 respectively).

The risk of dying from stomach cancer was higher among those employed in jobs 1, 2, or 4 for at least 12 months compared with those never so employed (relative risk = 1.29). This difference approached statistical significance.

The risk of dying from lung cancer was lower among those employed in jobs 4, 5, 6, or 7 in the tyre sector for at least 12 months compared with those similarly employed in the general rubber goods sector (relative risk = 0.92). This difference did not approach statistical significance.

FITTING OF MODELS

Cancer of the stomach

A simple model (appendix A) allowing for doubling dose was applied to mortality from cancer of the stomach in relation to duration of employment in the industry (irrespective of which departments were worked in). Results (maximum likelihood estimates) may be summarised as follows:

doubling dose (D): exposure (or insult) equivalent to that received in 40 years of employment in the industry (95% confidence limits 17–500 years).

The percentage of deaths from stomach cancer attributable to occupational exposure (including any synergistic effect with other factors), assuming the above model, was estimated by examining the excess

Table 11 Testing the null hypothesis of no effect from duration of employment in fume and/or solvent exposure jobs on mortality from cancer of the lung and bronchus over levels of controlling variables by the method of RMLT.† (Test factor = cumulative duration of employment in jobs 4, 5, 6, or 7)

Controlling variable	No of deaths	Mean difference in exposure§	Test statistic
By cohort:			
1946-50	713	+0.4	+1.70
1951-55	314	+0.1	+0.18
1956-60	164	+0.2	+0.46
By duration of employment (years):			
1-2	339	-0.2	-2.29*
3-7	319	+0.1	+0.81
≥8	533	+0.7	+1.86
By industry sector:			
Tyre	988	+0.5	+2.58**
General rubber goods	203	-0.7	-1.80
By years of follow up:			
1-9	197	+0.2	+0.87
10-19	384	+0.2	+1.00
≥20	610	+0.3	+1.18
Total	1191	+0.3	+1.65

†, §, || See footnotes †, §, || for table 10.

*p < 0.05; **p < 0.01.

risk predicted by the model for those dying from this disease (percentage attributable 18%, 95% confidence limits 2%-32%) (appendix B).

A more complex model allowing for cancer latency and doubling dose (appendix A) was applied to these data. Results (mle) may be summarised as follows:

- (1) doubling dose (D): exposure (or insult) equivalent to that received in 20 years of employment in the industry (95% confidence limits 8-100 years, given that L = 25 years).
- (2) optimum latent period (L): 25 years.

The percentage of deaths from stomach cancer attributable to occupational exposure (including any synergistic effects with other factors), assuming the above model, was similarly estimated (percentage attributable 23%, 95% confidence limits 7%-40%). The inclusion of this further variable (cancer latency) could not be justified on the grounds of statistical significance (simple model: maximum log likelihood 2.30; complex model: maximum log likelihood 3.44). (For each additional variable included in the model, an increase in log likelihood of 1.96 indicates statistical significance.)

The above models assumed a linear dose effect (exponent for non-linearity, E = 1.0). It was not possible to discriminate between values of 0.5 and 1.0 for this parameter. A value of 2.0 for this exponent tended to produce lower log likelihoods and could be excluded.

Similar models were applied for exposure estimated as duration of employment in dust jobs (jobs 1, 2, or 4). Maximum likelihood estimates were not statistically significantly different from zero.

Cancer of the lung

A simple model allowing for doubling dose was applied to mortality from cancer of the lung in relation to employment in jobs principally associated with fume and/or solvent exposure (jobs 4, 5, 6, or 7). This analysis was first carried out for the tyre sector. Results (mle) may be summarised as follows:

- doubling dose (D): exposure (or insult) equivalent to that received in 65 years of employment in jobs principally associated with fume and/or solvent exposure (95% confidence limits 32-400 years).

The percentage of deaths from lung cancer occurring among workers in the tyre sector and attributable to occupational exposure (including any synergistic effects with other factors), assuming the above model, was also estimated. (Percentage attributable 6%, 95% confidence limits 1%-11%.)

The above analysis did not include a variable allowing for cancer latency. When such a variable was included in the analysis, maximum likelihood estimates were as follows:

- (1) doubling dose D: exposure (or insult) equivalent to that received in 30 years of employment in jobs principally associated with fume and/or solvent exposure (95% confidence limits 15-125 years, given that L = 5 years).
- (2) optimum latent period (L): 5 years.

The percentage of deaths from lung cancer occurring among workers in the tyre sector and attributable to occupational exposure (including any synergistic effects with other factors), assuming the above model, was also estimated. (Percentage attributable

6%, 95% confidence limits 2%–11%.)

The inclusion of this further variable (cancer latency) could not be justified on the grounds of statistical significance, as the log likelihood (3.79) was only a little larger than that for the simpler model (3.16).

The above models assume a linear dose effect (exponent for non-linearity, $E = 1.0$). Other possible values of E could not be confidently excluded.

When the above analyses were repeated for the total study population (tyre and general rubber goods sector), maximum likelihood estimates were not statistically significantly different from zero.

Discussion

In the general population there is a steep positive social class gradient for mortality from all cancers and cancers of the stomach, oesophagus, and respiratory system and for many other sites of cancer.⁹ There is a negative social class gradient for certain other sites of cancer, melanoma and cancer of the testis, for example. It is, therefore, *not* surprising that compared with the general population this study cohort had an overall significant excess mortality from cancer of the stomach and cancer of the lung, nor it is surprising that compared with the general population there was a deficit of deaths from cancer of the testis. (There was also, in fact, low overall mortality from melanoma.)

The key question to be answered was this: given that the mortality experience of the cohort differed from that of the general population in several ways, were occupational factors concerned in the observed pattern of mortality? To address this question we used a method involving an internal standard (RMLT). The reasonableness of any approach using an internal standard depends on the main assumption that we are comparing like with like—namely, that after controlling for certain variables, such as year of hire, age at hire, exposed and non-exposed workers in a given year of follow up in a given subgroup are similar with respect to factors other than exposure. In this study cohort all were manual workers in one industry, and nearly all would have lived in the vicinity of their place of work.

The power of any mortality study must depend not only on the number of cause specific deaths available for analysis and on the method of analysis adopted, but also on the extent of discrimination in exposure within subcohorts. In this analysis, the “exposure” variables used were relatively crude but they merit consideration.

For the first exposure estimate (duration of employment in the rubber industry), it was not possible to control for any survivor population effect in the

data. This limitation would tend to produce negative test statistics. Such a statistic was indeed found for all causes of death, and could well imply that those less fit had left the industry earlier. This tendency increases the importance of the positive statistics found for cancers of the stomach, bladder, and liver.

For the remaining exposure estimates, it was possible to control for any survivor population effect in the data by stratifying over duration of employment in the industry. Nevertheless, one limitation of, say, the “dust exposure” estimates would be that some of the “non-exposed” jobs would also entail at least some exposure to dust. This would also, to some extent, work against the demonstration of any potential hazard. Also, if a carcinogen had only been present in certain departments for a few calendar years these exposure estimates would be unreliable.

Despite the above limitations, however, there was good evidence of involvement of occupational exposure in mortality from cancer of the stomach. Exposure to “fume” was not specifically implicated, whereas exposure to dust was, although the carcinogen or carcinogens involved may not be job-specific, as an overall significant finding was obtained only with exposure estimated as duration of employment in the rubber industry (irrespective of which departments were worked in).

Although the overall SMR for cancer of the oesophagus was 124 (table 5), no evidence has been found in the RMLT analysis to associate the observed excess mortality with occupational exposure. Our findings are not in agreement with those of Norell *et al.*, who recently reported a tenfold increased risk for oesophageal cancer among vulcanisation workers.¹⁰ We understand, however, that this latter group, although described as vulcanisation workers, were not employed in the rubber industry but were, in fact, employed repairing tyres in garages.

There was an association between duration of employment in jobs principally associated with fume and/or solvent exposure and mortality from cancer of the lung among workers in the tyre sector, but no such association among workers in the general rubber goods sector. Possible explanations for these discordant results include:

- (1) chance alone;
 - (2) a risk factor is present in the industry as a whole although job histories (defined in terms of 10 different jobs) for workers in the general rubber goods sector give no meaningful guide to levels of individual exposures to fume or solvents or both; and
 - (3) a risk factor associated with fume and/or solvent exposure is present in the tyre sector but not in the general rubber goods sector.
- We believe the second explanation to be more likely than the third.

Although the above association was found only in the tyre sector, it does not follow that workers in the tyre sector have a higher risk of lung cancer mortality than workers in the general rubber goods sector. The results presented in table 5 show, in fact, that this is not the case.

In the evaluation of the data relating to lung cancer it would clearly have been desirable to consider the possible influence of smoking. Unfortunately, information on smoking habit was not available. There is no good reason to believe, however, that smoking habit would correlate with duration of employment.

There was suggestive evidence of an occupational risk factor being present for cancer of the bladder among the first entry cohort, but no such evidence was found among the two later cohorts. This indicates that the withdrawal of recognised bladder carcinogens from production use in 1949 was successful in eliminating an occupational bladder cancer hazard.

A high SMR for the total study cohort was obtained for primary cancer of the liver (SMR = 172, based on 22 deaths), although the RMLT analyses produced no statistically significant findings for occupational exposures and mortality from this site of cancer. A recent cohort study of Swedish rubber workers also found an overall excess mortality from primary cancer of the liver among production workers ($O = 8$, $E = 2.0$).¹¹

It is not being suggested that any occupational hazards would operate precisely in the way predicted by the models that were fitted to the data. These models, however, provide our current best estimate of the size of risk factors that may have been present, as distinct from the earlier test statistics which merely indicate levels of statistical significance.

There are problems in fitting models to occupational cohort studies, particularly when occupational hygiene data are not available, resulting in wide confidence intervals around each estimated parameter. But the best estimate for the percentage of deaths from stomach cancer attributable to occupational exposures was 18%. This may be an overestimate as the corresponding SMR was only 115.

Similarly, the best estimate for the percentage of deaths from lung cancer occurring among workers in the tyre sector attributable to occupational exposures was 6%. This figure may, however, be an overestimate for the industry as a whole, as the RMLT analysis deliberately excluded that part of the study cohort in which it was known there was no effect—that is, the general rubber goods sector.

One interesting hypothesis relating to lung cancer that arises both from the model fitting exercise and from the observed trend in SMRs for lung cancer by period from first employment (table 6) is that for this

study cohort there may have been a risk factor present in the rubber industry acting on a late stage of the disease process, resulting in a relatively short interval between exposure and onset of the disease.

This study has provided further evidence of a causal association between the risks of lung and stomach cancer and occupational exposures.

Appendix A

FITTING MODELS

Simple model

Let x_j = duration of employment in particular kinds of jobs—for instance, dust jobs in follow up year j . This is an estimate of dose (or exposure or insult).

Let the relative risk in follow up year i be given by

$$R_i = 1 + \left(\sum_{j=1}^i \frac{x_j}{D} \right)^E$$

where D is the assumed doubling dose—that is, when the sum of the doses is D , the relative risk is 2, and where E is the exponent for non-linearity ($E = 1.0$ gives a linear dose response relation).

The model assumes that risk increases with increasing dose and does not allow for cancer latency.

The null hypothesis is that $\frac{1}{D} = 0$.

More complex model

Let exposure received k years ago have to be multiplied by a factor W_k to give the effective dose, where $W_k = k/L \exp(1 - k/L)$ and L is the optimum latent period in years.

For example, the figure shows W_k for $L = 20$ years.

W_k is less than 1.0 for all k except $k = L$, thus dose has maximum effect if received 20 years ago. This curve (equation) is being used because with one constant (L) the main features of any distribution of latent periods are probably being described—namely, no effect at $t = 0$ and $t = \infty$, and a maximum effect at some intermediate time $t = L$.

Let cumulative effective dose by follow up year i be Z_i

Latency factor.

where $Z_i = \sum_{j=1}^i W_{(i-j)}, x_j$

Let the relative risk in follow up year i be given by R_i ,

where $R_i = 1 + \left(\frac{Z_i}{D}\right)^E$

where D is the assumed doubling dose for exposure received L years ago, and E is the exponent for non-linearity.

Appendix B

ESTIMATING ATTRIBUTABLE RISK

Having obtained maximum likelihood estimates for the parameters of a model, calculate the risks—predicted by the model—for those who die from the cause of death under investigation.

Let n be the number of deaths, and the predicted relative risk be given by R_j where $j = 1, 2, \dots, n$.

The percentage attributable risk is estimated as

$$\frac{\sum_{j=1}^n (R_j - 1.0)/R_j}{n} \times 100 .$$

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