Brit. J. prev. soc. Med. (1954) **8**, 39–50

TUMOUR OF THE URINARY BLADDER AS AN OCCUPATIONAL DISEASE IN THE RUBBER INDUSTRY IN ENGLAND AND WALES

BY

R. A. M. CASE and MARGERY E. HOSKER*

The Chester Beatty Research Institute, Institute of Cancer Research, University of London

INTRODUCTION

During the investigations incidental to a large-scale survey of occupational tumours of the urinary bladder in males employed in a section of the British chemical industry (Case, Hosker, McDonald, and Pearson, 1954), it was found that men engaged in the manufacture of a certain rubber antioxidant of the primary aromatic amine class, which was used to a limited extent in the rubber industry, had suffered heavy casualties from bladder tumour. It therefore seemed desirable to see whether the risk of occupational tumour of the bladder extended into the rubber industry, and co-operation from this industry in the county borough studied was readily obtained. As soon as the trend of the investigation became apparent in 1949, the British manufacturers of the antioxidant voluntarily and promptly ceased to manufacture the product, and the British rubber industry ceased to use it and destroyed their existing stocks.

The antioxidant, which was a formaldehyde condensation product of alpha-naphthylamine and beta-naphthylamine, contained a small proportion (about 2·5 per cent.) of uncombined naphthylamines, and pilot experiments on a Banbury mixer showed that quantities of naphthylamines were vaporized during the processing of a rubber "mix" (Williams, 1949). In addition, the condensation process also led to the formation of 1:2:8:9-dibenzacridine (numbering according to the preferred system, Albert, 1951). This substance has been isolated from the antioxidant, and a highly purified synthetic speciment has been shown to be locally carcinogenic when injected subcutaneously into mice (Case, 1952).

HISTORICAL SURVEY

The concept of cancer (not specifically of the bladder) occurring as an occupational disease in the rubber industry is by no means new. This is illustrated by the following extract referring to the triennium 1929–31 (Registrar-General, 1938):

> Skilled Workers in Rubber (No. 207) returned a general mortality ratio of 110, with a probably significant excess for cancer (138). . . . The cancer excess of thirteen deaths was distributed over the buccal cavity and pharynx, 2; oesophagus and stomach, 5; skin, 2; and other sites, 4. A similar cancer excess was recorded in 1920–22. . . . There can be little doubt that the cancer excess has an occupational origin.
>
> The indices used are standardized mortality ratios (S.M.R.).

Bladder cancer as an industrial risk has also exercised the minds both of investigators and of the industry itself. Thus Hueper (1949) lists rubber occupations as being suspect on theoretical grounds, and both Schidrowitz (1944) and the Editor of the *India Rubber Journal* (1949) speculate about the possibility that phenyl-beta-naphthylamine in synthetic rubber and antioxidants made from alpha- and beta-naphthylamines in processed natural rubber might constitute a hazard.

It is also of interest to note that Dr. S. A. Henry, in a report to H.M. Senior Medical Inspector of Factories on a case of bladder tumour in the Chemical Industry, wrote as long ago as 1931:

> During my visit to the works I learned that naphthylamine is coming into considerable use in calico printing works and in rubber works, and this information may be helpful to us in our general investigation of the subject of occupational cancer of the bladder (Henry, 1931).

Falk, Steiner, Goldfein, Breslow, and Hykes (1951) and von Haam and Mallette (1952) isolated a series of carcinogenic aromatic hydrocarbons from processed rubber, and also from some carbon blacks used in rubber.

TECHNOLOGICAL HISTORY

Rubber technology is a vast and complicated subject, but fortunately only a few aspects of it now appear to be relevant to the present inquiry. Most of the rubber industry is concerned with the production of tyres. Barron (1947), to whose book the present authors are indebted for much of the technological history in this paper, states:

> . . . about 80 per cent. of all rubber is used in the motor industry, mainly for tyres . . . A large proportion

* Sometime Royal Cancer Hospital Research Scholar.

of the remainder goes into what are known as mechanical goods, which include such articles as belting, packings, moulded goods, hose and innumerable types of products.

Basically, the processing of the rubber for nearly all these products is similar.

The processing of the raw rubber includes mastication and the mixing in of chemical additives, followed by calendering. During these processes the mass is exposed to heat, and in many types of machinery any volatile matter can escape to the ambient atmosphere. The rubber "mix" is worked whilst hot to form the required product, usually by either extrusion or moulding, and the subsequent vulcanization is usually carried out in steam-heated autoclaves. Thus operatives working in the rubber mills, mixing department, calendering, moulding, extruding, curing, or vulcanizing processes will all be exposed to the chemicals added to the raw rubber.

If indeed the rubber industry offers a cancer hazard to workmen employed therein, and if the possibility that raw rubber itself is carcinogenic is rejected, then, in the present state of our knowledge of carcinogenic agents, the important additives which might be suspected of containing a carcinogenic factor or factors amongst them can be divided into three groups. Historically, the use of these three groups became widespread throughout the industry at different times:

(1) *Organic Accelerators.*—The discovery of the properties of accelerators was made *c.* 1906, though the use of organic accelerators only became "quite general and systematic" (Barron, 1947) after 1920.

(2) *Carbon Black Reinforcing Agents.*—The use of large quantities of gas-black as a reinforcing agent became general also about 1920.

(3) *Organic Antioxidants.*—These were introduced after 1925, becoming general towards the end of the decade 1920–29.

In addition to members of these groups, plasticizers, softeners, fillers other than carbon black, inorganic colouring materials, and organic dyestuffs may be added according to the nature of the final product. There seems at present no reason to suspect these compounds of being possessed of possible carcinogenic properties.

The organic accelerators cover a wide range of products, but may be broadly classified as consisting of aldehyde-amines, guanidines, carbon disulphide accelerators, and mixtures of members of these groups. The carbon blacks are obtained by a variety of processes, the essence of all of which is the incomplete combustion of some form of hydrocarbon. The antioxidants also cover a wide range of chemical products, which in some cases overlap the accelerator group and cannot all be clearly differentiated from it. They may be broadly classified as hydrocarbon waxes, phenols, primary aromatic amines, amino-phenols, phenolamine salts, aldehydeamines, secondary alkaryl-amines, substituted diphenylamines, secondary naphthyl-amines, acetoneaniline reaction products, and benzimid-azoles. Usually not more than one of these substances would be used in any one rubber "mix", many of them are in fact interchangeable, and the end results on the finished product might differ but slightly.

It is perhaps desirable at this stage to emphasize that there is no *a priori* reason to suspect all or many of the compounds listed above of being potentially carcinogenic. Two only, according to our present knowledge (*i.e.* in 1949), might be regarded as possibly able to give rise to a potential occupational bladder tumour hazard. One of these belongs to the aldehydeamine class and might contain or liberate free alpha-naphthylamine. The other, already mentioned in the introduction, is listed in the primary aromatic amine class (Barron, 1947), but could more properly be assigned to the aldehydeamine class, and might contain or liberate free alpha- and beta-naphthylamine, as well as containing 1:2:8:9-dibenza-cridine. Should benzidine, the antioxidant properties of which were discussed by Heywood (1943), come into wide-spread use, this also would constitute a potential hazard which would require consideration.

It is necessary to emphasize that, despite fairly intensive animal experiments (Hartwell, 1951), no evidence has been found to suggest that the substituted naphthyl-amines, such as the phenyl- or ethyl-naphthylamines, are in any way carcinogenic, and that so far clinical and statistical experience has not raised any suspicion of a hazard in the manufacture or use of these derivatives.

Scope of the Investigation

The particular antioxidant considered was introduced about 1927–28, but it is likely to have been the choice of only some firms. The hypothesis that this particular antioxidant introduces an occupational bladder tumour hazard requires the demonstration of an excessive number of bladder tumours in workmen engaged in rubber occupations, and this increase must persist or be enhanced in factories where the particular substance had been used. Furthermore, the excess should not be present in similar factories where the substance had not been used. These criteria, though necessary, are not both necessary and sufficient, since it would not be possible to reject absolutely the possibility that some other substance used was the causative agent.

The expected induction time of the tumours, if such do occur, may be expected to be of a similar character to that found in the chemical industry, that is about 18 years, with a standard deviation of 7 years, the distribution being normal and the parameters being unaffected by the intensity or duration of the exposure (Case and others, 1954). Very few tumours would be expected to have become manifest by 1935, after which date the rate of appearance would be expected to accelerate until about 1946, after which it should remain approximately constant unless the risk is abolished, when it should slowly subside after a further period of about 18 years.

If the hypothesis is true, it would be reasonable to expect that the excess cases would appear after 1935 and not be detectable before that time. This is not a necessary condition for the hypothesis, since it is theoretically possible that the anti-oxidant might have replaced another dangerous substance.

The relatively recent date of the expected occurrence of the occupational tumours would also mean that a high proportion of the cases developing will be still alive by 1951, the last year to be considered, since a fair proportion of the cases survive more than 5 years from the time of onset. This means that a study of the most accurate records available, namely death certificates, may not yet give conclusive evidence of the existence or, equally important, of the non-existence, of a risk.

These studies were directed therefore towards elucidating

(1) whether there is an increased risk of tumour of the bladder in workmen engaged in rubber occupations compared with the total male population of England and Wales;

(2) whether this risk persists in areas where the particular antioxidant under consideration is known to have been used;

(3) whether the risk, if it exists, shows a temporal change with 1935–36 as a pivotal point.

In view of the expectation of the survival time attenuating the value of death certificates as a criterion, morbidity figures have also been studied where possible.

Sources of Information and Methods Used

In the investigation of the occupational hazard in a section of the chemical industry (Case and others, 1954), no distinction was drawn between the condition sometimes described as "papilloma" of the bladder and carcinoma of the bladder, the two manifestations being considered as a disease entity, tumour of the bladder. This convention is adhered to in the present studies.

In this previous investigation the reality of the hazard was demonstrated by the use of a form of analysis that may conveniently be designated "comparative composite cohort analysis". This is a technique whereby the actual occurrence of an event in a population defined by individual name and working environment, with the age and date of entry into the environment, is observed, and the result compared with what would be expected from a "general population" or population not exposed to a specific risk of the event, observed for the same length of time. Thus the unit of the analysis is the cohort, which is defined by two or more characteristics, each defining a sub-cohort, *e.g.*, age, environment, and date of entry into environment. These sub-cohorts are later combined by summation of the expected frequency of the event, introducing the composite element.

The particular advantage of this type of analysis when applied to environmental problems is that much more data can be used than in the alternative techniques, since withdrawal from the environment does not affect the method of estimation. The method is an elaboration of the cohort principle discussed by Kermack, McKendrick, and McKinlay (1934) and Barclay and Kermack (1937), and subsequently developed further by Whelpton (1952) and Taylor (1952) for problems of fertility analysis.

The specific application of comparative composite cohort analysis to occupational tumours of the bladder for males in England and Wales, with Tables to facilitate the easy application of the method, has been discussed at length by Case (1953a, b). When applied to industrial hazards, however, this method presupposes the full and detailed co-operation of the industry concerned. In the previous investigation (Case and others, 1954) a prior appreciation of risk had secured this co-operation. In the present investigation there has been no prior appreciation of risk, and therefore this method of analysis was not feasible.

In the absence of the detailed information that would be required for the foregoing type of analysis, another less precise method is resorted to. This is the standard method used by the Registrar-General in the "Decennial Supplements, Occupational Mortality Tables", where a yearly estimate of the employed population in the relevant occupations is broken down into age groups, and from this an estimate of the expected frequency of the event under consideration is made by the application of the age-specific rates for that event determined for the general population. The determination of the observed number of events requires that the subject shall be in the specified environment at the time that the event takes place. Thus all the information that can be utilized is that relating to workers who, once having entered the specified occupation, remain in that occupation until the event being studied overtakes them. The increase of precision of the former method of analysis described above over this latter form will depend upon the labour stability of the industry concerned, but may easily be of the order of five-fold or more.

In the present studies the environment considered is defined by the list of rubber occupations in the Census, Occupation Tables (General Register Office,

1924, 1934), qualified further by the requirement that the occupation must have been an insurable occupation under the pre-1948 regulations (*i.e.* Unemployment Insurance Act) unless age was the sole condition not fulfilled. Assistance in allocating men to these occupations was obtained by the use of the "Classification of Occupations, 1950" (General Register Office, 1951). The event, in the mortality studies, is a death certificate mentioning tumour of the urinary bladder (*cf.* Case, 1953a), and in the incidence studies for the region specified, a hospital record of having suffered from tumour of the urinary bladder.

The sources of information available to us were:

(1) All death certificates mentioning tumour of the urinary bladder in males for England and Wales for the years 1921–51 inclusive.

(2) All cases of bladder tumour notified to us by, or found by us in the records of, all the hospitals in a large county borough for the years 1936–50 inclusive. The county borough was also one of the important centres of the rubber industry, and it was known that the particular antioxidant under consideration had been used there from 1928 to 1949.

Since it is uncommon for a case of tumour of the bladder not to be treated or investigated in a hospital at some time during the course of the disease, and since the standard of record keeping of the hospitals in this particular area since 1936 has been of above average efficiency, it is believed that an almost complete coverage of the area has been achieved. As some sort of a check on this belief, the data relating to persons normally resident within the county borough were abstracted, and the annual age-specific "report"* rates for the county borough calculated.

Similarly death certificates for persons normally resident within the county borough were abstracted from the national data, and the mean annual death certification rate (*cf.* Case, 1953a) was calculated for the same age groups for the same years. These figures are shown in Table I. In all age groups except the ultimate one, the "report" figures exceeded the certification figures (ignoring the age group under 25, where the rates are equal but the number of events very small, being only three in each case). This suggests that no serious deficit in reporting has occurred in any age group. The greater certification rate in the ultimate group is of course to be expected, since many of the cases will have been included in the "report" figures in earlier age groups.

A further check on the adequacy of the "report" figures can be obtained by using the completeness of death certification figures quoted by Case and others (1954) for co-operating hospitals throughout the country.

* "Report" in these studies is defined as those cases appearing in the hospital data, whether alive or dead, and whether actually reported by the hospital or found in the hospital records by us.

TABLE I

AGE-SPECIFIC CERTIFICATION RATES AND "REPORT" RATES FOR TUMOUR OF THE BLADDER (PER MILLION LIVING PER YEAR) CALCULATED FROM FIGURES FOR THE 15-YEAR PERIOD 1936–50

County Borough

Age	Death Certification Rate	Hospital "Report" Rate
Under 25	2·55	2·55
25–	2·55	13·91
35–	11·10	42·61
45–	78·88	160·46
55–	204·34	313·27
65 and Over ..	755·45	577·78
No. of Cases ..	602	809

Here it was shown that out of 819 patients "reported" who had since died, 81·3 per cent. had bladder tumour mentioned on the death certificate. If we apply this rate to the county borough in question, it is possible to calculate that since 602 death certificates were found for the 15-year period, 740 "reports" would have been necessary to obtain this number. If the survival time is assumed to have remained constant for the whole period of collecting all the cases, and if the increase of incidence discussed by Case (1953a) is ignored, then 740 "reports" should be expected in the 15-year period under discussion. In fact 809 reports were found, 109 per cent. of the expected number. This reasonably good agreement lends further support to the belief that the "report" rates are not seriously underestimated.

(3) Estimates of the male civil population by age groups for England and Wales for each year from 1921 to 1951 inclusive.

These were obtained from the appropriate copies of the "Statistical Review of England and Wales" (Registrar-General).

(4) An estimate of the mean annual male population by age groups for the county borough for the years 1936 to 1950.

These figures are based on the "1931 Census", the "1951 Census 1 per cent. samples" (General Register Office, 1934, 1952), the "1939 National Register" (National Register, 1944), and the "1947 Estimates of Sex and Age Distribution of the Civilian Population" (General Register Office, 1949). These figures were used in computing the age specific rates for the county borough discussed above.

(5) Estimates of the insured population employed in the rubber industry for each year from 1923 to 1951 for England and Wales, and for 1936 to 1950 for the county borough.

Some of these figures are published in various official sources, such as the different volumes of the "Abstracts of Statistics for the United Kingdom" (Central Statistical Office) and the remainder were provided by courtesy of the Ministry of Labour and National Service.

(6) The numbers engaged in the rubber occupations (as opposed to the rubber industry) for England and Wales, and also for the county borough, for 1921, 1931, and 1951.

"Census Reports", General Register Office (1924, 1934, 1952).

(7) The age composition of the population engaged in the rubber occupations for England and Wales for 1921, 1931, and 1951, and for the county borough for 1921.

"Census Reports", General Register Office (1924, 1934, 1952).

(8) Replies received to a questionary relating to occupational history sent to the hospital patients, or to a near relative, for the county borough.

Explicit written permission from the competent hospital authorities was obtained before this was done. The reply rate was about 30 per cent.

(9) Occupational histories as and when stated on the hospital records of the cases reported.

Not more than 20 per cent. of histories gave any occupation, and in very few cases was the information sufficiently explicit to be of any value.

(10) Replies received from the medical officer of one rubber factory in the county borough relating to specific queries about patients' occupational histories.

From these data it was possible to compute or extract the following information:

(*i*) All cases of bladder tumour, alive or dead, who may be assumed, from what is known of their occupational history from any source, to have come into contact with hot rubber during its processing, or to have worked on machines contaminated with the chemical additives. Only 52 of these 85 cases can be used statistically, but they are all set out *in extenso* in Table II (overleaf) as a record which may be of interest at some subsequent date. The cases in Table II may be subdivided into the following categories:

(*a*) The actual number of cases where the death certificate mentions tumour of the bladder where the deceased was employed in an insurable job (Unemployment Insurance Act Regulations) which is classified as a rubber occupation. These figures have been found for both England and Wales for the years 1921 to 1951 inclusive (35), for the same area for 1921 to 1935 inclusive (9), and for 1936 to 1951 inclusive (26). The similar figure has also been found for the county borough for 1936 to 1950 inclusive (5). This last figure is of course included in the national figures.

(*b*) The actual number (22) of cases of bladder tumour, alive or dead, "reported" from the hospitals of the county borough in the years 1936–50, where the patient or deceased at the time of the "report" was employed in an insurable (Unemployment Insurance Act Regulations) capacity in a rubber occupation, and was also normally resident within the county borough and employed therein. Since occupational histories could not be obtained for all cases "reported" this number may be a serious underestimate, but it cannot be an overestimate.

(*c*) The number (33) of cases found from national death certificates or "reported" where the deceased or patient was either a non-insurable rubber worker, a retired rubber worker, a rubber worker in a job not classified as a rubber occupation, or a person who had previously been employed as a rubber worker but who now had a different occupation.

In Table II the cases are arranged in chronological order of "reporting" or certification, and the category as described above to which they are allotted is designated by the letter *a*, *b*, or *c*.

(*ii*) Estimates of the insured male population engaged in the rubber occupations for each year. For England and Wales this is computed for the years 1921 to 1951 inclusive, and for the county borough for the years 1936 to 1950 inclusive. The estimates were made as follows:

(*a*) The basal figures used are the estimates of insured persons employed in the rubber industry mentioned above. The figures for 1949, 1950, and 1951 were multiplied by 0·89 to bring them into line with the pre-July 1948 figures, this being the date when the new National Insurance Act came into force. The factor 0·89 is the ratio of the June to July 1948 figures for the county borough, and the same factor is also used for the national figures in default of the June and July 1948 figures for England and Wales being available.

(*b*) The figures for 1921 and 1922 for England and Wales are taken as being the same as the figures for 1923, the first year for which the estimates are available.

(*c*) The figures thus obtained are now multiplied by a modifying factor which represents the ratio of males employed in the rubber occupations to those employed in the rubber industry. Managers are excluded. The figures could only be determined at three points, 1921, 1931, and 1951, the census years. No census was held in 1941 owing to the Second World War. The figures are respectively 0·57, 0·46, and 0·60. In each case these are derived from the information for England and Wales (or, in 1951, for Great Britain), and, in default of the specific figures being available, are regarded as being applicable to the county borough also. The 1921 figures

TABLE II

ALL WORKERS IN RUBBER OCCUPATIONS OR RUBBER INDUSTRY KNOWN TO HAVE HAD TUMOUR OF THE BLADDER

Date of "Report"	Index No.	Rubber Industry History (from all sources)	Age at Death	Age at "Report"	"Papilloma" P Carcinoma C	Category † *a*, *b*, or *c* (see text)	Within the County Borough
	1	Rubber worker	53	53	C	*a*	no
	2	Rubber works tyre dept	42	42	C	*a*	no
	3	Tyre cutter at rubber tube works	42	42	C	*a*	no
1921	4	Cutter in rubber hose pipe works	41	41	C	*a*	no
to	5	Labourer in electric cable works, rubber mix dept	69	69	C	*c*	no
1930	6	Rubber and leather manufacturer	68	68	C	*c*	no
	7	Rubber worker (retired)	70	70	C	*c*	yes
	8	Fabric preparing dept, tyre building factory 3 yrs	66	66	C	*a*	yes
	9	Mixer on rubber mill, tyre factory 5 yrs	58	58	C	*a*	yes
	10	Previously night watchman, rubber tyre factory	50	50	C	*c*	yes
	11	Foreman, rubber tyre factory	55	55	C	*a*	no
1931	12	Rubber worker	53	53	C	*a*	no
to	13	Rubber moulder	37	37	C	*a*	no
1935	14	Rubber worker (retired)	80	80	C	*c*	no
	15	Stoker, rubber factory	68	68	P	*c*	no
		Pivotal Point					
	16	Labourer, rubber works	77	77	C	*a*	no
	17	Foreman rubber worker, tyre factory	68	68	C	*a*	no
	18	Rubber hand	65	65	C	*a*	no
1936	19	Mechanical rubber worker	68	68	C	*a*	no
to	20	Rubber mixer	68	68	P	*a*	no
1940	21	Rubber worker, rubber mills	62	62	C	*a*	no
	22	Rubber worker (retired)	78	78	C	*c*	yes
	23	Air compressor attendant. Machine in tyre shed, rubber works, 23 yrs (retired)	—	67	P	*c*	yes
	24	Rubber mixer on mill, tyre factory 17 yrs	—	45	P	*b*	yes
	25	Previously labourer in rubber works, many yrs	—	61	P	*c*	no
	26	Foreman, rubber works	38	38	C	*a*	no
	27	Rubber worker	63	63	C	*a*	no
	28	Labourer, rubber works	63	63	C	*a*	no
	29	Labourer, rubber tyres	60	60	P	*a*	no
	30	Labourer, rubber works	65	65	C	*a*	no
	31	Rubber stamp manufacturer (retired)	72	72	C	*c*	no
	32	Manager, rubber works (retired)	71	71	C	*c*	no
1941	33	Labourer, rubber works (retired)	71	71	C	*c*	no
to	34	Foreman rubber worker (retired)	82	82	C	*c*	yes
1945	35	Mixer in rubber mill, tyre factory 20 yrs, death certificate gave only other causes	47	46	C	*b*	yes
	36	Tyre moulder 7 yrs, later tyre inspector (retired)	76	76	C	*c*	yes
	37	Rubber mixer, foreman, rubber mill 30 yrs	—	67	P	*b*	yes
	*38	Tube department, tyre factory 30 yrs	—	60	P	*b*	yes
	39	Foreman, tube dept, tyre factory 35 yrs	58	58	C	*a* and *b*	yes
	40	Rubber factory foreman, tyres, later soles, 22 yrs.	58	52	C	*a*	no
	41	Rubber tyre factory, 1912–15	—	56	P	*c*	yes
	42	Tyre factory, grinder in tool-room, 1920–30	54	53	C	*c*	yes
	43	Commissionaire, tyre factory, 1940–45	62	62	C	*c*	yes

TABLE II—*Continued*

ALL WORKERS IN RUBBER OCCUPATIONS OR RUBBER INDUSTRY KNOWN TO HAVE HAD TUMOUR OF THE BLADDER

Date of "Report"	Index No.	Rubber Industry History (from all sources)	Age at Death	Age at "Report"	"Papilloma" P Carcinoma C	Category † *a*, *b*, or *c* (see text)	Within the County Borough
	44	Rubber tyre worker	54	54	C	*a*	no
	45	Foreman, rubber tyre works	44	44	P	*a*	no
	46	Mat puncher, rubber mat manufacturers	65	65	C	*a*	no
	47	Labourer, motor tyre factory	44	44	C	*a*	no
	48	Rubber tyre maker's moulder	38	38	C	*a*	no
	49	Rubber worker	68	68	C	*a*	no
	50	Rubber pressman	66	66	C	*a*	no
	51	Ruber moulder	54	54	C	*a*	no
	52	Rubber hose cutter (retired)	75	75	C	*c*	no
	53	Rubber pressman (retired)	75	75	C	*c*	no
	54	Tyre builder, rubber works (retired)	76	76	C	*c*	no
	55	Rubber works, 1920–26	77	77	C	*c*	yes
1946	56	Rubber worker, 1919–24	—	54	P	*c*	no
to	57	Rubber mixer in mill 9 yrs	66	66	C	*a*	no
1951	58	Tyre cover maker 42 yrs	—	69	P	*b*	yes
(Eng-	59	Tyre moulder, many years	—	51	P	*b*	yes
land	60	Rubber worker, tyre factory 30 yrs	—	58	P	*b*	yes
and	61	Rubber moulder, tyre works 30 yrs	—	48	C	*b*	yes
Wales)	62	Rubber worker, tyre-works 37 yrs	—	57	P	*b*	yes
	63	Rubber moulder, tyre factory 2 yrs	—	49	P	*b*	yes
	64	Rubber worker, tyre factory 30 yrs	—	60	C	*b*	yes
	65	Rubber worker, tyre factory 13 yrs	—	33	C	*b*	yes
	66	Rubber moulder, tyre factory 29 yrs	—	59	P	*b*	yes
and	67	Rubber mill, mixer, tyre factory 28 yrs	—	55	C	*b*	yes
	68	Rubber moulder, tyre factory 38 yrs	59	59	C	*a* and *b*	yes
	69	Previously labourer in rubber works, many yrs	—	63	P	*c*	no
	70	Tube extruder, tyre factory 24 yrs	—	45	P	*b*	yes
	71	Rubber worker, rubber mill (retired at time of death but not of "report")	72	69	C	*b*	yes
1946	72	Rubber moulder, tyre factory, 1924–26	—	50	P	*c*	no
to	*73	Vulcanizer, tyre factory 33 yrs	—	58	C	*b*	yes
1950	74	Previously in elastic thread dept, rubber works 1 yr	—	27	P	*c*	yes
(Coun-	75	Rubber works labourer 30 yrs	62	62	C	*a* and *b*	yes
ty Bo-	76	Rubber moulder, tyre factory 27 yrs	51	51	C	*a* and *b*	yes
rough)	77	Rubber moulder, tyre factory, 1919–41	—	62	C	*c*	no
	78	Pipe fitter, 1929–41, tyre factory	67	66	P	*c*	yes
	79	Maintenance man, tyre factory, 1919–32	—	62	P	*c*	yes
	80	Engineer, mainly research and development, tyre and golf-ball factory, 1937–41	—	36	P	*c*	yes
	81	Works engineer, tyre factory	—	62	C	*c*	yes
	82	Pipe-fitter, 1918–22, tyre factory	—	67	P	*c*	yes
	83	Rubber moulder, 1940–41	—	54	P	*c*	yes
	84	Maintenance engineer, rubber works	68	68	C	*c*	no
	85	Rubber moulder, tyre factory 18 yrs	36	36	C	*a* and *b*	yes

*These two patients noted that several other men in the same department were suffering from the same complaint.

†Total Category *a*: 35; Total Category *b*: 22 (including five common to *a* and *b*); Total Category *c* (not used in statistical studies): 33.

are used for the decade 1921–30, the 1931 figures for the decade 1931–40, and the 1951 figures for the decade 1941–50, and also for the year 1951. The use of modifying factors derived at long intervals results in some discontinuity of trend, and it is unfortunate that the 1931 figure was obtained at a time of severe industrial depression. The original figures for insured workers in the rubber industry show a discontinuity between 1930 and 1931; this discontinuity is magnified by the change of the modifying factor from 0·57 to 0·46 at the end of the decade. The crude figures do not show a discontinuity between 1940 and 1941, though one is introduced by the change of the modifying factor in the rubber occupations figures. It is thus possible that towards the end of the decade 1931–40 the population at risk has been underestimated by as much as 24 per cent. However, since the expected number of death certificates for the rubber occupations in England and Wales at the risk current for the general population for the half decade 1936–40 is estimated as 2·7 on the figures used, the 24 per cent. underestimate would be only 0·65, and this amount would not affect the final conclusions.

The same discontinuity between 1940 and 1941 is introduced into the figures for the county borough, but the error which might be introduced by underestimation for the years 1936–40 would amount to 0·33 cases in the expected estimate, which could not affect the conclusions.

(*d*) The figures are now finally adjusted to age-specific figures. At the present stage of adjustment they are limited to men under 65. These figures are broken down into age groups by using the percentage age-distribution for 1921 for the decade 1921–30, 1931 for 1931–40, and 1951 for 1941–50, and also for 1951, the calculated proportion of men aged over 65 being added to the total figures. The national figures for England and Wales are used for the county borough in default of the specific figures being available. However, in 1921, when the county borough figures were available, they showed a very marked similarity to the national figures. The age distribution figures are shown in Table III.

It is recognized that this adjustment has followed a tenuous argument, and relies to some extent upon the demographic structural stability of the industry during each decade, and also upon the assumption that the part of the industry in the county borough is a reasonable cross section of the industry as a whole. Such published figures as are available suggest that in fact both these conditions obtain to such a degree that the estimates are sufficiently good for the present purpose. Could the estimates of the population at risk be shown to be sufficiently erroneous, and it is possible that data may later become available to enable the figures to be reviewed, then the statistical conclusions of these studies would be invalidated. Therefore the total finally adjusted figures for England and Wales are shown in full in Table IV. The figures for the county borough are not shown here but, as will be shown later, the discrepancy between the actual findings and the expected findings in this area are so great that it would seem unlikely that an error can have been introduced which would be sufficient to invalidate the conclusions referring to the county borough.

TABLE III

PER CENT. AGE DISTRIBUTION OF MALE WORKERS IN RUBBER OCCUPATIONS

Area	Year	Age					
		Under 25	25–	35–	45–	55–	65 and Over
England and Wales	1921	28·4	26·6	20·8	14·3	7·4	2·6
	1931	26·4	31·3	19·6	13·1	7·6	2·1
	1951	11·8	29·8	31·9	15·9	7·6	3·0
County Borough	1921	21·2	29·6	25·4	15·6	5·1	2·1

TABLE IV

ESTIMATED NUMBERS OF MALE WORKERS IN RUBBER OCCUPATIONS WHO WOULD HAVE BEEN INSURABLE UNDER PRE-1948 (UNEMPLOYMENT INSURANCE ACT) REGULATIONS, OR WHO WOULD HAVE BEEN DEBARRED FROM BEING INSURABLE SOLELY BECAUSE OF BEING OVER 65

England and Wales

Year	Number	Year	Number	Year	Number
1921	16,611	1931	15,379	1941	23,684
1922	16,611	1932	15,355	1942	19,306
1923	16,611	1933	15,819	1943	17,235
1924	16,979	1934	15,777	1944	18,205
1925	17,447	1935	16,759	1945	18,743
1926	17,488	1936	16,542	1946	23,892
1927	18,067	1937	16,693	1947	29,413
1928	19,043	1938	16,111	1948	31,658
1929	19,786	1939	17,280	1949	30,932
1930	20,213	1940	17,984	1950	33,171
				1951	36,261

(*iii*) The age-specific certification rates (*cf.* Case, 1953a) for males in England and Wales by decades from 1921–50. These are shown in Table V.

TABLE V

AGE-SPECIFIC CERTIFICATION RATES (PER MILLION LIVING PER YEAR) FOR MALE DEATH CERTIFICATES MENTIONING BLADDER TUMOUR, CALCULATED FROM DECENNIAL FIGURES, ENGLAND AND WALES

Age	Decennium		
	1921–30	1931–40	1941–50
Under 25 ..	0·38	0·22	0·26
25–	1·92	1·89	1·37
35–	10·66	10·61	11·10
45–	47·30	54·95	63·58
55–	160·67	166·86	210·24
60 and Over ..	445·12	477·36	562·41

(*iv*) The age-specific certification rates and "report" rates for the county borough for the years 1936–50. These have already been shown in Table I.

(*v*) The number of death certificates mentioning tumour of the bladder that would have been expected to occur in the populations at risk in England and Wales, and also in the county borough during the relevant periods had the disease occurred at the rate pertaining for the general male population of these areas respectively.

(*vi*) The number of cases of bladder tumour that would have been expected to have been "reported" from the hospitals of the county borough from the population at risk had the cases occurred at the rate pertaining for the general male population of the county borough.

Results

(1) England and Wales.—Table VI shows the number of bladder tumour death certificates found and expected for males in the rubber occupations in England and Wales during the periods 1921–35 and 1936–51. Since the numbers found can only be integers, it is assumed that sampling errors may be expected to conform to the Poisson distribution, and the significance of the difference on this hypothesis is shown. The figures are also expressed as a standardized mortality ratio (S.M.R.) in conformity with the practice of the Registrar General in the extract from the "Occupational Mortality Tables" quoted in the historical section. This S.M.R. is the number of deaths found per 100 deaths expected.

Table VI

COMPARISON OF THE NUMBER OF MALE DEATH CERTIFICATES MENTIONING TUMOUR OF THE BLADDER EXPECTED AND FOUND IN THE RUBBER OCCUPATIONS AS DEFINED FOR 1921–35 AND 1936–51, ENGLAND AND WALES

Period	1921–35		1936–51	
Number	Expected	Found	Expected	Found
	8·5	9	15·9	26
Standardized Mortality Ratio		106		164
Significance of Difference *P*	> ·1		< ·025	

Assuming the validity of the population at risk estimates, these figures must be interpreted as showing that an excess of deaths from bladder tumour has occurred in men engaged in rubber occupations in England and Wales during the period 1936–51, and that no such excess was demonstrable in the period 1921–35. This excess is statistically significant.

(2) The County Borough

(*a*) *Death Certificates.*—Table VII shows the number of bladder tumour death certificates found and expected for males in rubber occupations in the county borough during the period 1936–50. The significance of the difference and the S.M.R. are also shown. Although the S.M.R. is higher than the national figure for 1936–51, the small number of cases concerned is too small for the difference between the numbers found and expected to be regarded as statistically significant.

Table VII

A COMPARISON OF THE NUMBER OF DEATH CERTIFICATES MENTIONING TUMOUR OF THE BLADDER EXPECTED AND FOUND IN THE RUBBER OCCUPATIONS AS DEFINED FOR THE YEARS 1936–50

Males. The County Borough

Number	Expected	Found
	2·6	5
Standardized Mortality Ratio		192
Significance of Difference, *P*	·1	

(*b*) *Hospital "Reports".*—Table VIII shows the number of cases, alive or dead, found and expected in the hospital "reports" for males engaged in the rubber occupations in the county borough during the years 1936–50. The significance of the difference and the standardized "report" ratio (S.R.R.) is shown. The standardized "report" ratio is used in the same way as, and with a homologous meaning to, the S.M.R. Again assuming the validity of the estimates of the population at risk, and also that the "report" rates are not seriously underestimated, these figures must be interpreted as showing a gross excess of cases of bladder tumour found over cases

Table VIII

A COMPARISON OF THE NUMBER OF "REPORTED" CASES OF BLADDER TUMOUR EXPECTED AND FOUND IN THE RUBBER OCCUPATIONS AS DEFINED FOR THE YEARS 1936–50

Males. The County Borough

Number	Expected	Found
	4·0	22
Standardized Mortality Ratio		550
Significance of Difference *P*	< ·001	

expected. It seems an extremely remote possibility that the errors in forming the estimate of the expected number could be sufficiently great to invalidate the result, since the figure for the estimate would have to be increased to about fifteen, *i.e.* to nearly four times its present value, before the difference between the expected number and the number found would cease to be statistically significant. This would imply that, even if the number of workers in the rubber occupations equalled the figures given for the rubber industry (the limiting case), then the hospital "reports" would have to be less than 50 per cent. of the true incidence for the area, and further would have to be so biased that all the rubber worker cases were included in the 50 per cent. that were in fact "reported"! There is no reason to believe that any such bias for rubber cases being "reported" would exist, and, as was mentioned previously, the figure of 22 cases found is likely to be an underestimate because of the number of hospital "reports" where no occupation is known.

It would thus seem that the statement that there is a definite excess of cases of bladder tumour in workers in the rubber occupations in the county borough can be made with considerable confidence.

Discussion

This investigation was undertaken with a specific object in view, to see whether the introduction of a certain rubber antioxidant into the rubber industry could have given rise to an industrial hazard of occupational tumour of the urinary bladder. On the hypothesis that it had done so, and that no such risk had been present before, or had been introduced contemporaneously, it would be expected that no risk could be demonstrated before a date about 10 years after the introduction of the hazard, that the national figures might show the presence of a risk subsequently to this, and that this risk would persist or be enhanced in areas where the particular substance had been used, since, being a substance not unique in its industrial properties, and manufactured only by certain firms, there would be no reason to expect its use to be evenly spread throughout the country. The results obtained—that a risk is demonstrable in the national figures (deaths only) since a date about 7 years after the introduction of the particular antioxidant into the rubber industry, and that this risk persists (live and dead cases) and is in fact enhanced in an area where the substance was known to have been used—are compatible with the truth of the hypothesis, but they are in no sense a proof of its truth. Many critical factors have not been examined because the data required for their examination were not available. For instance, it would be essential for the acceptance of the hypothesis to show that no risk had appeared in areas of the rubber industry where the particular substance had never been introduced, and it would be desirable to find exactly what processes were affected in the areas where it had.

It is perhaps apposite to quote the words of Anscombe (1951):

> It is worthwhile to distinguish the different purposes one may have in accepting a hypothesis: (*i*) to base an administrative decision on, (*ii*) for further testing and confirmation, (*iii*) for acceptance into the corpus of scientific knowledge, to be relied on in future work.

In the present case, it is not suggested that the hypothesis should be accepted for purpose (*iii*); it is suggested that it could be regarded as sufficiently acceptable on the evidence produced to form a basis for planning an investigation under heading (*ii*), and that until this investigation has been planned and executed it should be accepted as sufficiently true for certain decisions under heading (*i*).

A word of caution is necessary about the possible extrapolation of the results reported herein. The substance considered was manufactured in Great Britain by a process that left some uncombined amine in the finished product. Methods of manufacture used elsewhere may not leave this uncombined fraction. The results reported here apply to England and Wales and to a county borough situated in one of these countries. It does not follow, therefore, that the hazard shown by these studies will necessarily exist elsewhere, and negative findings in other countries should not be regarded as invalidating these results.

Leaving, for a moment, the statistical considerations which have been the subject of this paper so far, and considering the 85 cases listed in Table II, of which only 52 can be used in the statistical section, it is worthwhile noting that cases have occurred in workers employed in care and maintenance work and in jobs that would bring them into considerable contact with departments where rubber occupation proper would be pursued (*e.g.*, an air-compressor attendant who worked a machine for many years while it was situated in a tyre manufacturing department). Whilst of course no evidence has been presented that all or any of these tumours amongst these ancillary workers are of occupational origin, it should be remembered that cases which were regarded as occupational were noted in workers in ancillary jobs of a like nature in the survey of a section of the chemical industry (Case and others, 1954).

Furthermore, in the county borough, forty patients worked or had worked in one factory, and two letters received from rubber workers in answer to the questionary mentioned that the sender had thought it remarkable that several men (five and seven were quoted, six were traced) working in the patient's own particular shed were attending hospital for treatment for the same complaint (these two observations referred to the same shed and the same men). This number is greater than the number of cases expected for the whole county borough. These observations suggest that there may be local areas of risk where the incidence is raised further above the expected level than is suggested by the overall figures. This phenomenon of a very high risk around the actual dangerous process was noted by Hueper (1948) as one of the criteria of environmental hazard, and further detailed investigation might well show this type of incidence to be present in the rubber industry.

Another feature of Table II is the number of patients still alive. Unless it is postulated that the occupational cases tend to have a longer survival time than the non-occupational ones, a phenomenon not reported by Case and others (1954), for the chemical industry, this would suggest that the outbreak of occupational tumour of the bladder in rubber workers has been noted in an early stage. If the causal agent can be located with certainty, and either removed or its effects prevented, then the outbreak may never assume the serious proportions that might otherwise follow.

Since insufficient evidence exists as yet to distinguish the occupational cases from the non-occupational ones in Table II, no studies have been attempted in relation to the induction time of the occupational disease within the rubber industry, and no attention has been paid to the age at onset or at death.

Summary and Conclusions

(1) There seems to be reasonably good statistical evidence for saying that, in the period between 1936 and 1951, an occupational risk of dying of bladder tumour can be demonstrated amongst males in England and Wales who are employed in the rubber occupations as defined by the "1931 Census Reports, Occupation Tables" (General Register Office, 1934).

(2) There is even better statistical evidence for saying that in a certain county borough, which is an important centre of the rubber industry, there is an occupational risk of contracting bladder tumour amongst males so employed. This evidence covers the years 1936–50.

(3) There is no statistical evidence even to suggest that such an occupational risk of dying of bladder tumour was operating amongst males in these occupations in England and Wales in the period 1921–35.

(4) These findings are consistent with, but do not prove, the hypothesis that the risk was introduced into the industry with a certain antioxidant in 1928. This antioxidant was used in the rubber industry in the county borough studied. It was known to have caused bladder tumours amongst men in the chemical industry who manufactured it. The antioxidant concerned, as manufactured in Britain, contained about 2·5 per cent. of free naphthylamine, including a proportion of both the alpha and beta isomers, and it is known that the treatment accorded to the rubber "mix" containing the antioxidant volatilizes quantities of naphthylamines.

(5) When the trend of these studies became known, the manufacturers of the antioxidant voluntarily ceased its manufacture and withdrew it from their range of products, and the rubber industry immediately discontinued the use of the antioxidant and destroyed old stocks.

(6) Cases of bladder tumour have also been noted in fitters, engineers, and others in ancillary jobs in the rubber industry who might be expected to have intermittent contact with contaminated machinery. No statistical data are available to enable an opinion to be formed about the possible occupational origin of these cases.

It would be a pleasure to acknowledge individually and by name the many people in the hospitals and the rubber industry in the county borough, on whose close co-operation the success of much of the investigation depended. Since the county borough has remained anonymous, we have not done this; but we hope that these invaluable helpers will recognize themselves and accept our sincere thanks for untold hard work, assistance, and encouragement.

It is a pleasure to acknowledge the equally invaluable help that we have received from the staff of the Registrar-General, from Dr. E. R. A. Merewether, H.M. Senior Medical Inspector of Factories, Ministry of Labour and National Service, from Drs. J. M. Davidson and J. Watkins Pitchford, respectively Principal and Senior Medical Officers of the Ministry of National Insurance, and from Miss Drever B. McDonald and Miss Joan T. Pearson of the Chester Beatty Research Institute.

References

Albert, A. (1951). "The Acridines". Arnold, London.
Anscombe, F. J. (1951). *Mind*, 60, 299.
Barclay, R. S., and Kermack, W. O. (1937). *Proc. roy. Soc. Edinb.*, 58, 55.
Barron, H. (1947). "Modern Rubber Chemistry", 2nd ed. Hutchinson, London.
Case, R. A. M. (1952). Unpublished report.
—— (1953a). *British Journal of Preventive and Social Medicine*, 7, 14.

—— (1953b). *Brit. J. industr. Med.*, **10**, 114.
——, Hosker, M. E., McDonald, D. B., and Pearson, J. T. (1954). *Ibid.*, **11**, 75.
Central Statistical Office (various years) "Annual Abstract of Statistics (U.K.)", Labour Tables. H.M.S.O., London.
Falk, H. L., Steiner, P. E., Goldfein, S., Breslow, A., and Hykes, R. (1951). *Cancer Res.*, **11**, 318.
General Register Office (1924). "Census of England and Wales, 1921." Occupations, Tables 2 and 8. H.M.S.O., London.
—— (1934). "Census of England and Wales, 1931." Occupations, Table 2. H.M.S.O., London.
—— (1949). "Estimates of the Sex and Age Distribution of the Civilian Population . . . 1947." H.M.S.O., London.
—— (1951). "Classification of Occupations, 1950", p. 81, *et seq.*, H.M.S.O., London.
—— (1952). "Census 1951 Great Britain", ONE per cent. Sample Tables, Part I, p. 52 *et seq.* H.M.S.O., London.
Haam, E. von, and Mallette, F. S. (1952). *Arch. industr. Hyg.*, **6**, 237.
Hartwell, J. L. (1951). "Survey of Compounds which have been tested for Carcinogenic Activity", 2nd ed., pp. 97, 103, and 104. Federal Security Agency, Public Health Service Publication No. 149. U.S. Govt. Printing Office, Washington.
Henry, S. A. (1931). Unpublished report.
Heywood, M. M. (1942). *Institution of the Rubber Industry Transactions*, **18**, 181.
Hueper, W. C. (1948). "Environmental and Occupational Cancer", p. 14. Publ. Hlth Rep. Suppl. 209. Government Printing Office, Washington.
—— (1949). *Industr. Hyg. Newslett.*, 9, No. 12 (December), 7.
India Rubber Journal, Editorial (1949). *India Rubb. J.*, **116**, 9.
Kermack, W. O., McKendrick, A. G., and McKinlay, P. L. (1934). *Lancet*, **1**, 698.
Kiser, C. V. (1952). *J. Amer. statist. Ass.*, **47**, 25.
National Register (1944). "Statistics of Population . . . 1939." H.M.S.O., London.
Registrar-General (various years). "Registrar-General's Statistical Review of England and Wales." Tables, Part II, Civil: Population Tables, 1921–1951. H.M.S.O., London.
—— (1938). "Registrar-General's Decennial Supplement, England and Wales, 1931." Part IIa. Occupational Mortality, p. 121. H.M.S.O., London.
Schidrowitz, P. (1944). *Rubb. Age (N.Y.)*, **54**, 428.
Taylor, W. (1952). *British Journal of Social Medicine*, **6**, 226.
Whelpton, P. K. "Cohort Fertility: Native White Women in the United States" (Unpublished). *Cited by* Kiser (1952).
Williams, M. H. C. (1949). Personal communication.