REVIEW

Cancer risk in the rubber industry: a review of the recent epidemiological evidence

Manolis Kogevinas, Maria Sala, Paolo Boffetta, Neely Kazerouni, Hans Kromhout, Shelia Hoar-Zahm

Abstract

***Objectives*—To examine the recent epidemiological evidence on cancer risk among workers in the rubber industry.**

***Methods*—Epidemiological studies published after the last detailed review by the International Agency for Research on Cancer (IARC) in 1982 were reviewed. 12 cohort studies in nine countries that examined distinct populations of workers in the rubber industry, seven industry based nested case-control studies, 48 community based case-control studies in 16 countries, and 23 studies based on administrative data that reported risks for employment in the rubber industry were identified.**

***Results*—Excess risks of bladder cancer, lung cancer, and leukaemia were found in most studies, with risks above 1.5 in about half of the studies. A moderate excess risk for laryngeal cancer was consistent across studies. Excess risks were found in a few studies for cancers of the oesophagus, stomach, colon, liver, pancreas, skin, prostate, kidney, brain, and thyroid, and for malignant lymphoma and multiple myeloma, but overall results were not consistent for these neoplasms.**

***Conclusions*—Magnitude of the observed risks varied considerably between studies, but overall the findings indicate the presence of a widespread moderate increased cancer risk among rubber workers. The most consistent results were for bladder, laryngeal, and lung cancer and for leukaemia. Excess risks were also found for other neoplasms but an evaluation of the consistency of the findings is difficult because of the possible selective reporting of results. Recent studies do not provide information associating specific exposures with cancer risk. The preventive measures taken in the rubber industry in recent years may decrease risks, but this has not been documented yet in epidemiological studies.**

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Respiratory and Environmental Health Research Unit, Institut Municipal d'Investigació Mèdica, Barcelona, Spain
M Kogevinas
M Sala

Unit of Environmental Cancer Epidemiology, International Agency for Research on Cancer, Lyon, France
P Boffetta

Occupational Epidemiology Branch, National Cancer Institut, Bethesda, USA
N Kazerouni
S Hoar-Zahm

Department of Environmental and Occupational Health, Wageningen Agricultural University, Wageningen, The Netherlands
H Kromhout

Correspondence to:
Dr M Kogevinas, Respiratory and Environmental Health Research Unit, Institut Municipal d'Investigació Mèdica (IMIM), 80 Doctor Aiguader Road, Barcelona 08003, Spain. Tel: 0034 3 2211009; Fax: 0034 3 2213237; Email: KOGEVINAS@IMIM.ES

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The evidence of a carcinogenic risk in the rubber industry has been reviewed by the International Agency for Research on Cancer (IARC) in 1982[1] and in summary form in 1987.[2] The IARC Working Group[1] concluded that there was sufficient evidence that employment in this industry entails a carcinogenic risk. This association was considered causal for bladder cancer and leukaemia, whereas confounding could not be ruled out for the excess risks found for stomach and lung cancer. The strength of the evidence was considered to be limited for cancer of the skin, prostate, and colon, and for lymphoma and inadequate for cancer of the brain, thyroid, and pancreas.

Examination of processes or exposures within this industry was pre-empted at the time of the IARC evaluation, because of the limited information available. The early studies of rubber workers in the United Kingdom[3 4] showed a large increase in the risk of bladder cancer among workers employed during the 1930s and 1940s, which was attributed to exposure to β-naphthylamine. Subsequent studies have shown that removal of this agent led to a decreased cancer risk.[5–7] It was postulated that heavy exposure to dusts such as carbon black in the first steps of production lines may be associated with the risk of stomach cancer, and that the risk of lung cancer was associated with exposure to curing fumes. In the United States, a large study of rubber workers employed in two companies in Ohio, showed little or no excess of bladder cancer,[8 9] whereas there was a suggestion of an increased risk of stomach cancer, possibly related to exposure to talc,[10] of prostate cancer,[11] and lymphatic leukaemia,[12] possibly associated with exposure to solvents, particularly benzene.

Recent exposures in the rubber industry

Since the early 1950s and more extensively since the 1970s, health and safety measures have been widely applied in the rubber industry by substituting some chemical agents and controlling exposure to others.[13] A recent extensive exposure survey in the rubber industry in The Netherlands, did not find the large differences in the past in exposure to airborne particulates between front processing (weighing and mixing, calandaring, extruding) and back processing (curing and vulcanising).

Table 1 Summary data on cohort studies and studies based on asministrative data in the rubber industry published after 1982

Author	*Description of study*
Cohort studies:	
Holmberg *et al* 1983[15]	Sweden, two factories. 13114 workers. Mortaltiy 1961-78. Three exposure groups: (*a*) mixers/weighers, (*b*) other production, (*c*) white collar. Same factories as Gustavsson *et al* 1986.[16] Both sexes.
Gustavsson *et al* 1986[16]	Sweden, two factories. 8374 workers. Mortality 1952-81. Cancer incidence 1959-80. Minimum employment is one year. Same factories as Holmberg *et al* 1983.[15]
Norseth *et al* 1983[17]	Norway, 2448 men employed for 18 months or more in a footwear and tyre plant between 1953-78. Cancer incidence. Workers classified in five departments.
Delzell and Monson 1984[18]	USA, Akron, Ohio. 6533 men employed in the industrial products division of a rubber plant (BF Goodrich). Mortality 1940-78. Same cohort as Delzell and Monson.[19-21]
Delzell and Monson 1984[19]	USA, Akro, Ohio. 3161 men employed in the aerospace division of a rubber plant (BF Goodrich). Mortality 1940-78. Same cohort as Delzell and Monson.[18 20 21]
Delzell and Monson 1985[20]	USA, Akron, Ohio. 1152 white men in the tyre-curing department of a rubber plant (BF Goodrich). Mortality 1940-78. Same cohort as Delzell and Monson.[18 19 21]
Delzell and Monson 1985[21]	USA, Akron, Ohio. 1970 white male reclaim workers of a rubber plant (BF Goodrich). Mortality 1940-78. Same cohort as Delzell and Monson.[18-20]
Wang *et al* 1984[22]	China, two tyre factories in Shanghai. Both sexes. Incidence of cancers of the lung, stomach and liver, 1971-80. Workers classified in five departments.
Sorahan *et al* 1986[23]	UK, BRMA cohort, 36445 male rubber workers. Mortality 1946-80. Minimum employment is one year. Workers classified into tyre and general rubber goods sector; by exposure to dusts; by exposure to fumes or solvents.
Sorahan *et al* 1989[24]	UK, as in Sorahan *et al* 1986. Mortality 1946-85.
Veyes *et al* 1991[25]	UK, 16450 workers. Cancer incidence 1946-85. One of the tyre plants included in the BRMA cohort, see also corrigendum.[26]
Bernardinelli *et al* 1987[27]	Italy, tyre manufacturing factory. 4917 male non-office workers. Mortality 1962-83.
Negri *et al* 1989[28]	Italy, 6629 male workers in rubber tyre factory. Mortality 1946-81. Five job categories.
Zhang *et al* 1989[29]	China, Shanghai, 1624 employees in a rubber factory. Both sexes. Mortality from lung cancer 1972-84. Classification of workers by type of job and by exposure to curing agents or talc powder. Adjustment for smoking.
Szeszenia *et al* 1991[30]	Poland, 6978 male workers of a rubber goods factory, mainly footwear. Mortality 1945-85.
Carlo *et al* 1993[31]	Texas, USA, 2306 male workers in a tyre manufacturing plant employed for at least one year between 1962 and 1989. Exposure levels reported to have been minimal compared with older cohorts.
Solionova and Smulevich 1993[32]	Russia, Moscow, 1178 men and 2492 women employed at a rubber footwear and other rubber goods plant for at least 10 years before 1983. Cancer incidence and mortality. Workers classified into production/non-production.
Weiland *et al* 1996[33]	Germany, 11663 male rubber workers. Mortality 1981-91. Employment minimum one year, hired between 1910-91.
Studies based on administrative data:	
Norell *et al* 1983[91]	Sweden, record linkage study, 1961-73. Vulcanisation workers. SIR.
Malker *et al* 1987[92]	Sweden, record linkage study, 1961-79. Rubber industry. SIR.
Olsen and Jensen 1987[93]	Denmark, record linkage study, 1970-9, 76985 cases. Rubber industry. SPIR.
Zheng *et al* 1992[94]	China, Shanghai, 1980-84. Rubber and plastic workers. SIR.
Dolin and Cook-Mozaffari 1992[95]	England and Wales (selected regions), 1965-80. Rubber workers. SIR.
Linet *et al* 1993[96]	Sweden, record linkage study, 1961-79. Rubber manufacturing workers. SIR.
Pukkala *et al* 1995[97]	Finland, record linkage study, 1970-85. Rubber products workers. SIR.
Hrubec *et al* 1995[98]	USA, 1954-80. Rubber workers. Comparative mortality figure (CMF).
Costa *et al* 1995[99]	Italy, Turin, record linkage study, 1981-9. Tyres and rubber production. SMR.

SIR = standardised incidence ratio; SPIR = standardised proportional incidence ratio; SMR = standardised mortality ratio.

Replacement of powdered chemicals by chemicals in non-powdered form led to reduced exposures to inhalable particulates in the compounding mixing area. However, 22% of almost 60 different accelerating, retarding, and antidegrading agents were still being used in powdered form by the end of the 1980s, including several agents classified in either the British Rubber Manufacturers Association B (acute or chronic toxic effects), or Sc (carcinogenic effects) categories. Exposure to solvents was generally low and restricted to workers involved in pretreating. The median fumes concentration in curing departments was as high as 400 mg/m^3. Dermal exposure to compounds soluble in cyclohexane was high for workers in engineering services and in compound mixing departments.[13] When the same companies were revisited five years later in 1994, the chemicals in the Sc category had been either replaced, cut down in use, or used in non-powdered form.[14]

This review

In this review we summarise the evidence on cancer risks from cohort and case-control studies and from studies with administrative data published after the 1982 IARC evaluation, and examine whether these studies provide more detailed information on the role of specific agents in determining cancer risk. We reviewed studies on the sectors of the rubber industry evaluated by IARC in 1982: tyre manufacturing and repair, cable making, and manufacture of other rubber goods. Studies of workers in the production of natural rubber and synthetic polymers are excluded.

Materials and methods

Studies were identified through literature searches in commercial data banks (MEDLINE, CANCERLINE, TOXLINE), IARC archives, and in the United States National Cancer Institute computerised reference file. We did not include unpublished data and studies reported only as abstracts. We identified 12 cohort studies from nine countries examining distinct populations of workers in the rubber industry[15–33]; seven nested case-control studies in this industry[34–40]; 48 distinct community based case-control studies from 16 countries that used questionnaire data and reported risks for employment in the rubber industry[41–90]; and finally, 23 studies based on administrative data[91–113]—such as death certificates, cancer registration, or linkage between census and cancer registry—that presented results by industry or occupation pertinent to assess the risk of cancer among rubber workers. Some of the studies reviewed are updates or more specific investigations of previously reported cohorts.[18–21 23 24 35–40]

All studies are briefly described (table 1 (cohort) and table 2 (case-control)). In some studies, the populations examined partially

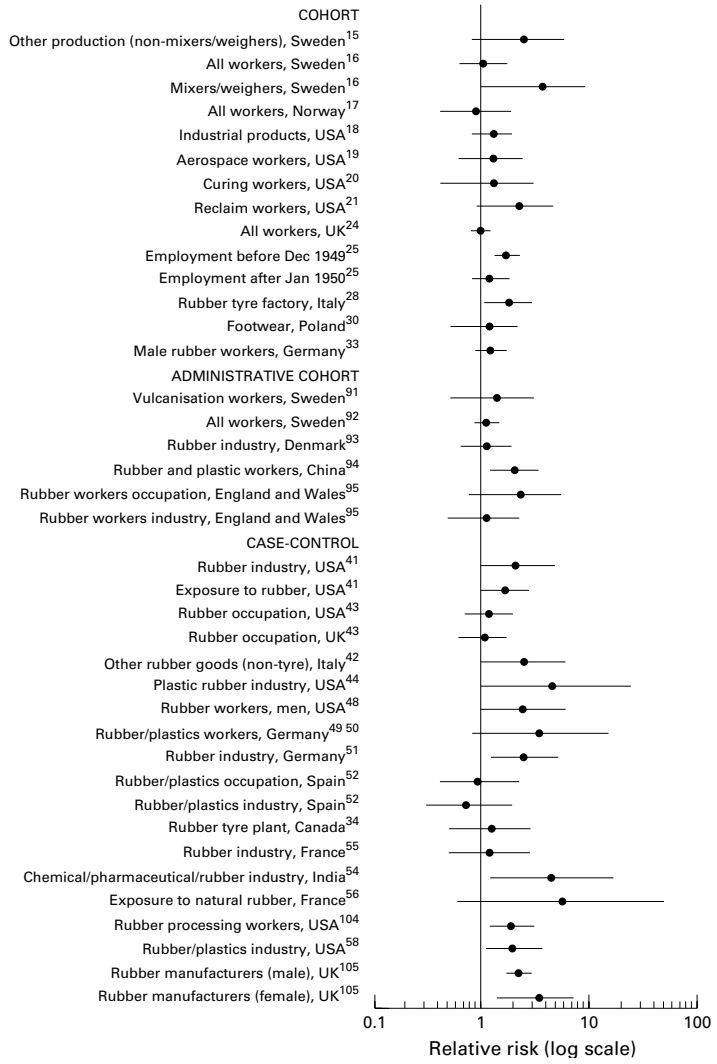

Figure 1 Bladder cancer risk in workers employed in the rubber industry. Odds ratios (95% CIs) for studies including >5 exposed cases.

overlap (tables 1 and 2). Studies are ordered chronologically, grouping subsequent reports of the same study population. We did not further consider in this review, case-control or proportional mortality rate (PMR) studies based on fewer than two exposed cases and controls or those not presenting quantitative risk estimates.[47 53 61 62 100] Studies based on administrative data are clearly noted and are presented with the cohort studies (studies presenting standardised mortality ratios (SMRs), standardised incidence ratios (SIRs), or rate ratios) or with the case-control studies (studies presenting case-control type statistics or PMRs). Studies based on administrative data are often limited in the precision of the measure of exposure which often refers to one point in time (census or death), and, in some cases, in statistical power. Also, preferential reports of positive or significant results may be a problem in these studies. Results from those studies are, therefore, reported only for neoplasms of the bladder, lung, stomach, and lymphatic and haematopoietic tissue. Results for workers in four distinct departments of the BF Goodrich, Akron, Ohio cohort (hereafter noted as the Akron, Ohio cohort), have been published separately[18–21] and are also reported separately in this review. In the text we make complete reference to all studies included in this review. In the accompanying summary figures (figs 1–5), we have only plotted the results of studies with >5 observed cases (cohort studies) or exposed cases (case-control studies), together with those identifying significant results (positive or negative). A detailed report is available from the authors.

Results

ALL CAUSES OF DEATHS AND ALL MALIGNANT NEOPLASMS

Mortality from all causes was higher than expected based on national reference rates in three cohorts.[15 24 33] Mortality was lower than expected in four studies[27 28 30 31] and in the four departments of the Akron, Ohio cohort.[18–21] Cancer incidence or mortality was higher than expected in six cohorts[15 24–28 30 33] and in the aerospace, curing, and reclaim departments of the Akron, Ohio cohort.[19–21] The excesses in SMRs or SIRs were mostly between 5% and 20%. Cancer incidence or mortality was lower than expected in four cohorts[17 22 31 36] and in the industrial process division of the Akron, Ohio cohort.[18]

BLADDER CANCER

Figure 1 shows the results on incidence and mortality of bladder cancer.

Cohort studies

Excess risk of bladder cancer was found in seven distinct studies[15–17 27 28 30 32 33] and in the four departments of the Akron, Ohio cohort,[18–21] either for the total study population or for workers employed in specific departments. A >50% excess risk, ranging from 1.6 to 5.2, was found in six of these studies and in the reclaim department of the Akron, Ohio cohort.[15–17 21 28 32] No excess risk was found in two studies.[24 31] In four studies reporting results by calendar period, risk was highest among workers employed before the 1950s[16 18 28 30] who, in one study, were potentially exposed to β-naphthylamine.[30] Risk of workers first employed after the 1960s was examined in three studies.[27 31 33] A twofold excess risk was found in the largest study (SMR 2.14, 95% confidence interval (95% CI) 1.07 to 3.84, 11 deaths).[33] The other two studies had little statistical power to examine bladder cancer risk. Only some studies reported risk in subgroups of workers[15–17 24] and there is no clear indication of a particular risk in any specific department of the rubber industry, or in workers of specific rubber products. An excess risk was found in five distinct studies based on administrative data[91–95] but no excess was seen in three.[97–99]

Case-control studies

Excess risks with odds ratios (ORs) ranging from 1.5 to 5.7, after adjustment for potential confounding factors such as smoking, were found in 11 case-control studies.[41 42 44 46 48 49 54 56 58 103] Lower excess risks were found in two community based studies[43 55] and in a nested case-control study[34] and no excess

Table 2 Summary data on case-control studies and studies based on administrative data in the rubber industry published after 1982

Author	*Description of study*
Bladder cancer:	
Schoenberg *et al* 1984[41]	USA, New Jersey, 658 bladder cancer cases; 1258 population controls. Lifetime occupational history. Partly overlapping with Zahm *et al* 1987.[44]
Coggon *et al* 1984[100]	England and Wales, 291 cases who died of bladder cancer. Two controls per case from all causes of death selected from death certificate. Usual occupation from death certificates.
Vineis and Magnani 1985[42]	Italy, Torino, 512 male bladder cancer cases; 596 male hospital controls. Lifetime occupational history.
Morrison *et al* 1985[43]	US, Boston; UK, Manchester; Japan, Nagoya. 430, 399, and 226 bladder cancer cases respectively; 397, 493, and 443 population controls respectively. Occupational history from questionnaire.
Baxter and McDowall 1986[101]	England; Six London areas, 1080 male cases; two controls per case (*a*) selected from deaths from all other cancers; (*b*) deaths from all causes. Mortality 1968-78. Occupations from death certificate.
Zham *et al* 1987[44]	USA, 2982 cases, 5782 population controls. Lifetime occupational history. Partly overlapping with Schoenberg *et al* 1984.[41]
Jensen *et al* 1987[45]	Denmark, Copenhagen, 371 bladder cancer cases; 771 population referents. Lifetime occupational history.
Schifflers *et al* 1987[46]	Belgium, 74 bladder cancer cases; 205 population controls. Lifetime occupational history.
Iscovich *et al* 1987[47]	Argentina, La Plata, 117 cases; 117 hospital and 117 neighbourhood controls. Three occupations of longest duration and most recent occupation.
Risch *et al* 1988[48]	Canada, 826 bladder cancer cases. 792 population controls. History of occupational exposures and jobs.
Claude *et al* 1989[49 50]	Germany, 531 male bladder cancer cases; 531 hospital controls. Lifetime occupational history. Same study as Kunze *et al* 1992.[51]
Kunze *et al* 1992[51]	Germany, 675 bladder cancer cases and hospital controls. Lifetime occupational history. Same study as Claude *et al* 1989.[49 50]
Gallagher *et al* 1989[102]	See entry under multiple cancer sites.
Gonzalez *et al* 1989[52]	Spain, five areas, 497 bladder cancer cases; 530 hospital controls, 530 population controls. Lifetime occupational history.
La Vecchia *et al* 1990[53]	Italy, Milan, 263 bladder cancer cases; 287 hospital controls. Checklist of occupations and exposures.
Choi and Nethercott 1991[34]	Canada, proportionate mortality study. 6208 workers in rubber tyre manufacturing plant. Mortality 1917-83.
Hall Rosenman 1991[103]	See entry under multiple tumour sites.
Notani *et al* 1993[54]	See entry under multiple tumour sites.
Cordier *et al* 1993[55]	France, 765 cases; 765 hospital controls. Lifetime occupational history.
Hours *et al* 1994[56]	France, Lyon, 116 cases. Two hospital control groups of 116 subjects each. Lifetime occupational history.
Barbone *et al* 1994[57]	Italy, north-east, 273 male and female cases; 573 hospital controls. Usual occupation.
Burnett *et al* 1994[104]	USA, 23 states. 8644 white male cases who died of bladder cancer. Proportional mortality study. Usual occupation from death certificates.
Swanson and Burns 1995[58]	See entry under multiple tumour sites.
Roman and Carpenter 1996[105]	UK, England, 1981-7, 16666 cases. Occupation from cancer registry records. Proportional registration ratio.
Lymphoma:	
Wilkosky *et al* 1984[35]	See entry under multiple tumour sites.
Bernard *et al* 1987[59]	UK, Yorkshire, Hodgkin's disease. 248 cases, 489 hospital controls. Lifetime occupational history.
Schumacher and Delzell 1988[106]	USA, North Carolina, 501 white and 1988 black male cases who died of non-Hodgkin's lymphoma; 569 death certificate based controls selected from all other deaths. Mortality 1968-70, 1975-77, and 1980-2. Usual occupation and industry from death certificates.
Persson *et al* 1989[60]	Sweden, Orebro, 54 cases of Hodgkin's disease; 106 cases of non-Hodgkin's lymphoma. 275 population referents. Checklist of occupational exposures.
La Vecchia *et al* 1989[61]	Italy, Milan, both sexes. Hodgkin's disease, 69 cases; non-Hodgkin's lymphomas, 153 cases; 396 hospital controls frequently matched. Checklist of occupations and exposures.
Francheschi *et al* 1991[62]	Italy, north-east, Pordenone province. 152 cases; 613 hospital controls. Checklist of occupations and exposures.
Blair *et al* 1993[63]	USA, Iowa and Minnesota, 622 white non-Hodgkin's lymphoma male cases; 1245 population based white male controls. Lifetime occupational history.
Multiple myeloma:	
La Vecchia *et al* 1989[61]	Italy, Milan, 110 cases; 396 frequency matched hospital controls. Checklist of occupations and exposures.
Heineman *et al* 1992[107]	Denmark, 1098 men diagnosed between 1970-84; 4169 controls chosen randomly from the Danish central population registry. Lifetime occupational history from pension fund records.
Pottern *et al* 1992[64]	Denmark, 363 women diagnosed between 1970-84; 1517 controls selected from the central population registry. Lifetime occupational history from pension fund records.
Demers *et al* 1993[65]	USA counties in Washington State; metropolitan Atlanta; metropolitan Detroit, 693 cases diagnosed between 1977-81; 1683 population based controls. Lifetime job history.
Figgs *et al* 1994[108]	USA, 24 states. 12148 male and female deceased subjects cases; 60740 controls dying from diseases other than cancer, selected from the death certificate data base. Mortality 1984-9. Occupation and industry from death certificate.
Leukaemia:	
Arp, Jr *et al* 1983[36]	USA, nested case-control study within a cohort of rubber industry workers (McMichael *et al* 1975).[12] 15 male and female cases of lymphocytic leukaemia; 30 matched industry controls. Mortality 1964-73. Historical solvent exposure profile for rubber industry job titles.
Wilkosky *et al* 1984[35]	See entry under multiple tumour sites.
Dubrow and Wegman 1984[109]	See entry under multiple tumour sites.
Flodin *et al* 1987[61]	Sweden, middle and south east, 111 white men and women diagnosed with chronic lymphatic leukaemia; 431 randomised population referents. Checklist of occupational exposures.
Malone *et al* 1989[67]	USA; western Washington State; northern Utah; Detroit, Michigan; Atlanta, Georgia, 427 men and women diagnosed with chronic lymphocytic leukaemia 1977-81; 1683 population based controls. History of chemical exposure and employment of six months or more in four specific industries.
Gallagher *et al* 1989[102]	See entry under multiple cancer sites.
Loomis and Savitz 1991[110]	USA; 16 states, 5147 male deceased subjects with leukaemia; 51470 controls (other causes of death). Subjects from 1985-7 mortality data tapes from the National Centre for Health Statistics (NCHS). Occupation from death certificate.
Lung cancer:	
Delzell *et al* 1982[37]	USA, Akron, Ohio (University of N Carolina cohort, McMichael *et al* 1975),[12] nested case-control study. 121 white male cases; 448 controls who died of other causes. Mortality 1964-73. Detailed employment history in 19 work areas.
Milne *et al* 1983[111]	USA; California, Alameda County, 925 lung cancer deaths; 6420 deaths with other cancers identified through death certificates. White and non-white males and females. Mortality 1958-62. Usual occupation and industry from death certificate.
Dubrow and Wegman 1984[109]	See entry under multiple tumour sites.
Wilkosky *et al* 1984[35]	See entry under multiple tumour sites.
Coggon *et al* 1984[100]	UK, England and Wales, 598 cases who died of lung cancer. Two controls per case from all other deaths selected from death certificate. Usual occupation from death certificate.
Kjuus *et al* 1986[68]	Norway, southeast, 176 male cases and 176 hospital controls. Main lifetime occupations or exposures.
Schoenberg *et al* 1987[69]	USA, six areas of New Jersey, 763 white male incident cases; 900 general population controls. Lifetime occupational history.
Andjelkovich *et al* 1988[38]	USA, University of North Carolina, nested case control study. 40 lung cancer cases occurring 1977-8; 148 controls. 20 occupational title groups.
Levin *et al* 1988[70]	China, Shanghai, 733 male cases; 760 population controls. Lifetime occupational history.

Table 2 continued

Author	*Description of study*
Gallagher *et al* 1989[102]	See entry under multiple tumour sites.
Burns and Swanson 1991[71]	USA, Michigan, Detroit metropolitan area, 5935 male and female cases; 3956 incident colon and rectum cancer referents. Complete occupational history.
Jockel *et al* 1992[72]	Germany, Bremen, Hamburg, Hannover, Cologne, and Bielefeld, 194 incident male and female cases; 194 hospital and 194 population controls. Lifetime history of occupation and occupational exposures.
Brownson *et al* 1993[73]	USA, Missouri. 429 white female incident cases aged 30 to 84 years; 1021 population based female controls. Checklist of selected occupations, industries and occupational exposures.
Notani *et al* 1993[54]	See entry under multiple tumour sites.
Wu-Williams *et al* 1993[74]	China, Shenyang and Harbin, 965 female cases; 959 population controls. Lifetime occupational history.
Swanson and Burns 1995[58]	See entry under multiple tumour sites.
Wang *et al* 1995[112]	China, Tianjin, cancer registry based case-control study. 8401 male and female lung cancer cases; 27695 cancer control. Current or more recent occupation at the time of registration.
Stomach:	
Gallagher *et al* 1989[102]	See entry under multiple tumour sites.
Coggon *et al* 1990[75]	UK, 95 male and female cases; 190 community controls. Lifetime occupational histories.
Gonzalez *et al* 1991[76]	Spain, four areas, 354 histologically confirmed male and female cases; 354 hospital referents. Lifetime occupational history.
Cocco *et al* 1994[77]	Italy, six areas, 640 histologically confirmed male cases; 959 population controls. Three longest held jobs.
Ward *et al* 1994[113]	USA, 24 states, white women deceased from cancer of the gastric cardia (n=128), cardia/lower oesophagus (n=162) and other gastric (n=6065); five controls per case randomly selected from deaths from other causes except cancer and gastrointestinal disorders. Mortality 1984-89. Occupation/industry from death certificate.
Colon:	
Peters *et al* 1989[78]	USA, Los Angeles County, 147 white men cases (72% colon and 28% rectal cancer); individually matched neighbourhood controls. Lifetime occupational history.
Swanson and Burns 1995[58]	See entry under multiple tumour sites.
Liver:	
Swanson and Burns 1995[58]	See entry under multiple tumour sites.
Larynx:	
Zagraniski *et al* 1986[79]	USA, Connecticut, New Haven, 92 white male cases diagnosed between 1975-80; 181 hospital controls. Lifetime occupational history.
Muscat *et al* 1991[80]	USA, New York, Illinois, Michigan, and Pennsylvania, 194 white male cases; 184 age matched hospital controls. Six longest held occupations.
Skin:	
Bourguet *et al* 1989[39]	USA, Akron, Ohio, 65 white male rubber workers with squamous cell carcinoma of the skin between 1964-81; 254 matched controls, workers in four major American rubber manufacturing companies. Lifetime occupational history.
Prostate:	
Wilkosky *et al* 1984[35]	See entry under multiple tumour sites.
Elghany *et al* 1990[81]	USA, Utah, 358 cases; 679 population controls. Longest and most recent industry/occupation.
Le Marchand *et al* 1991[82]	USA, Hawaii, Oahu, 452 cases; 898 population controls. Lifetime occupational history.
Kidney and renal pelvis:	
McLaughlin *et al* 1987[83]	USA, Minneapolis, St Paul metropolitan area, 74 white male and female cases diagnosed between 1974-9; 697 population controls. Usual occupation and checklist of exposures.
Partanen *et al* 1991[84]	Finland, 338 white men and women diagnosed between 1977-8; 484 matched population referents. Lifetime occupational history.
Central nervous system:	
Symons *et al* 1982[40]	USA, Ohio, Akron. Nested case control study in a plant of manufacturing rubber products, University of N Carolina cohort (Andjelkovic *et al* 1976,[9] McMichael *et al* 1976[10]). 22 brain and central nervous system cases. Controls from the plant. Mortality 1952-71. Complete work history.
Burch *et al* 1987[85]	Canada, southern Ontario, 215 men and women diagnosed with brain tumour between 1979-82; 215 hospital controls. History of occupations.
Preston-Martin *et al* 1989[86]	USA, California, Los Angeles County, 272 black and white men with a primary brain tumour first diagnosed during 1980-4; 272 matched neighbour controls. Detailed occupational histories.
Multiple tumour sites:	
Wilkosky *et al* 1984[35]	USA, nested case-control study within 6678 cohort members of rubber and tyre manufacturing plant, Akron, Ohio (University of North Carolina cohort, McMichael *et al* 1974[8]). Cases of lung, stomach, prostate, lymphatic, and haematopoietic neoplasms dying between 1964-73. Controls, 20% random sample of cohort. Exposure to 20 specific solvents.
Hall and Rosenman 1991[103]	USA, New Jersey state cancer registry, 1979-84. Proportional cancer incidence study. Results on rubber production reported only for bladder, liver, uterine cancer, and melanoma out of 38 distinct cancer sites examined. Occupational history from registration record.
Notani *et al* 1993[54]	India, Bombay, male cases of lung cancer (n=246) and bladder cancer (n=153); 212 male cancer controls. Lifetime occupational history.
Swanson and Burns 1995[58]	USA, Michigan, Detroit, women. 2015 lung cancer cases; 1558 colon cancer; 627 bladder cancer, 157 liver cancer. 1972 population controls. Lifetime occupational history. Same cases as Burns and Swanson 1991.
Dubrow and Wegman 1984[109]	USA, Massachusetts, 34879 deaths, 1971-3. Rubber workers. Standardised mortality odds ratio. Occupational history from death certificates.
Gallagher *et al* 1989[102]	Canada, BC, 1950-84. 320423 deaths. Proportional mortality ratio. Occupational exposure from death certificates.

SIR = standardised incidence ratio; SPIR = standardised proportional incidence ratio; SMR = standardised mortality ratio.

in three.[45 52 57] Exposure groups in most case-control studies were defined on the basis of lifetime occupational history and referred to employment in the rubber industry. In some studies, the exposed group included workers employed in the rubber and plastics industry,[52 44 58 49 103] or in even wider industrial areas.[46 54] In the study by Cordier *et al*,[55] no excess risk was found among workers employed during the period of use of β-naphthylamine. Two studies based on administrative data, in England and the United States, found an excess risk[104 105]; one study found no excess risk.[101]

NEOPLASMS OF THE LYMPHATIC AND HAEMATOPOIETIC TISSUE

Figure 2 shows the results on neoplasms of the lymphatic and haematopoietic tissue.

Malignant lymphomas

Cohort studies—Excess risks ranging from 1.7 to 3.6 were found in two cohort studies in Italy (Hodgkin's disease only)[27] and Norway[17] and in the industrial products and aerospace departments of the Akron, Ohio cohort.[18 19] Excess risks were found in various jobs or departments. No excess risk was found in two cohort

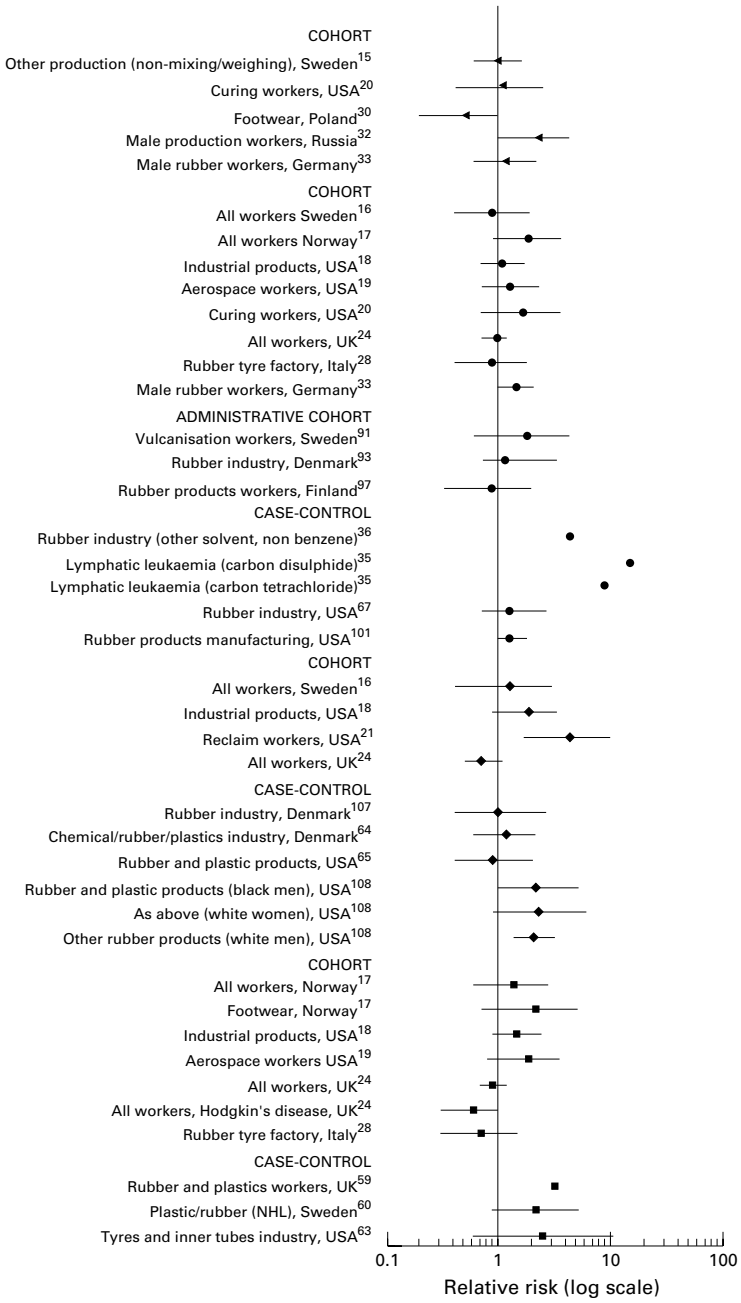

Figure 2 Risk of leukaemia (●), malignant lymphomas (■), multiple myeloma (♦), and unspecified neoplasms of the lymphatic and haematopoietic tissue (▲) in workers employed in the rubber industry. Odds ratios (95% CIs) for studies including >5 exposed cases.

studies[24 28] and in one study based on administrative data.[96]

Case-control studies—Excess risk of non-Hodgkin's lymphoma was found in two case-control studies among workers employed in the tyre and inner tubes industry[63] or in the rubber and plastics industry.[60] Excess risk for Hodgkin's disease was found in one study[59] but no excess risk was found in another.[60] An excess risk was also found in one study that used administrative data.[106]

Multiple myeloma

Cohort studies—Excess risks ranging from 1.3 to 4.3 were found in one Swedish study[16] and in the industrial products and reclaim departments of the Akron, Ohio cohort.[18 21] No excess was found in one study.[24]

Case-control studies—No excess risk was found in one study.[65] A twofold excess risk was found among men and women in three studies that used administrative data.[64 107 108]

Leukaemia

Cohort studies—Moderately increased leukaemia risks ranging from 1.5 to 2.3 were found in three cohort studies,[17 27 33] and in the tyre curing department of the Akron, Ohio cohort in the United States.[20] Lower excess risks were seen in the industrial products and aerospace departments of the Akron, Ohio cohort.[18 19] No excess risk was found in four cohort studies[16 24 28 31] and in the reclaim department of the Akron, Ohio cohort.[21] The risk of leukaemia was not centred in specific departments, and in most studies was not examined in relation to exposure to specific agents. In the Norwegian cohort,[17] six out of nine leukaemia cases had documented exposure to glues with a concentration of up to 4% benzene. An excess risk, ranging from 1.2 to 2.9, was found in three studies based on administrative data,[91 93 99] but no excess was found in two.[97 98]

Case-control studies—High excess risks associated with exposure to benzene[36] or other solvents[35 36] were found in two nested case-control studies within rubber industry cohorts. Excess risks lower than 1.5 were found in two case-control studies.[66 67] An excess risk was found in three studies based on administrative data.[102 109 110]

Unspecified lymphatic and haematopoietic neoplasms

Results were presented jointly for lymphoma and leukaemia in three cohort studies.[15 30 32] A twofold excess risk was found in the study from Russia.[32] Results were presented jointly for lymphomas and multiple myeloma in two cohort studies, in which no excess risk was found.[31 33]

LUNG CANCER

Figure 3 shows the results on lung cancer.

Cohort studies

Excess risks (ranging from 1.7 to 3.3) were found in four cohort studies[15 16 29 30 32] and in the curing department of the Akron, Ohio cohort.[20] These risks were found in a variety of departments including workers in tyre curing departments, mixing and milling, vulcanisation workers, and in one study in jobs with high exposure fumes or solvents. Excess risks <1.5 were found in two studies[24 33] and in the aerospace department of the Akron, Ohio cohort.[19] No excesses were found in the remaining four cohort studies[17 27 28 31] and in the industrial products and reclaim departments of the Akron, Ohio cohort.[18 21] In two cohorts, risk was highest among workers employed before the 1950s.[16 20] In studies including workers first employed after 1960, no excess was found in two studies,[27 31] whereas a small excess (SMR 1.36, 95% CI 1.04 to 1.75, 60 deaths) was found in the German study.[33]

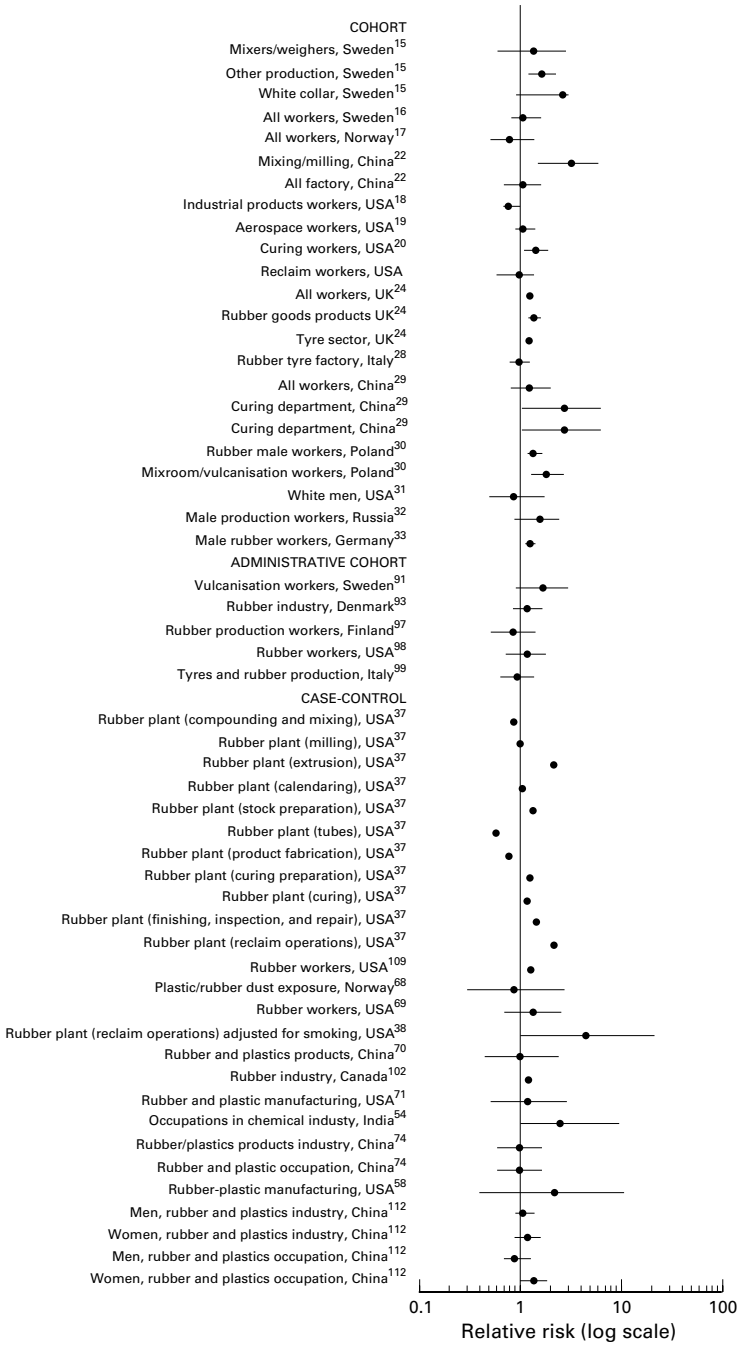

Figure 3 Lung cancer risk in workers employed in the rubber industry.

The smoking habits of a subgroup of workers were examined in one study[29] and the findings suggested that the excess risk of lung cancer could not be attributed to smoking. Risks ranging form 1.2 to 1.75 were found in three administrative data studies,[91 93 98] whereas no excesses were found in two record linkage studies.[97 99]

Case-control studies

Excess risks ranging from 1.5 to 4.6 were found in three community based studies[54 58 73] and in two nested case-control studies.[37 38] Lower excess risks were found in two studies,[69 71] and no excess risks were found in four community based studies.[68 70 72 74] No association was found with exposure to solvents in a nested case-control study.[35] In seven studies[54 58 68 70–72 74] the exposed group included workers in the rubber and plastics industry. An excess risk was found in four studies based on administrative data.[102 109 111 112]

STOMACH CANCER

Figure 4 shows the results on stomach cancer.

Cohort studies

Low excess risks not exceeding 1.6 were found in seven studies.[16 22 24 27 32 33] The risk was concentrated in the mixing and milling departments in two studies,[16 22] and in jobs with high exposure to dust in the British Rubber Manufacturers Association, United Kingdom cohort.[24] No excesses were found in four studies[17 28 30 31] and in the industrial products, curing, and reclaim departments of the Akron, Ohio cohort.[18 20 21] In none of the four studies based on administrative data that reported results for stomach cancer was the risk >5%.[91 93 98 99]

Case-control studies

Risk of stomach cancer was associated with long term manual employment in the rubber industry in an English study (OR 3.5),[75] and with exposure to rubber or talc in a Spanish study (OR 1.65).[76] A lower excess risk was found in one study which examined exposure of workers in the rubber or chemical industries.[77] In one study based on administrative data the risk was not >5%,[102] and in another study the risk depended on the position of the tumour.[113]

CANCER OF THE OESOPHAGUS

Cohort studies

An increased risk (SMR 2.7) of neoplasms of the oesophagus was found among reclaim workers in the Akron, Ohio cohort.[21] Lower risks, not >1.5, were found in three cohort studies,[24 30 33] the excess being significant in one study[24] (SMR 1.2, 95% CI 1.0 to 1.5). No excess risks were found in three other cohort studies[16 28 32] and in the industrial process division of the Akron, Ohio cohort.[18]

COLON CANCER

Cohort studies

A low excess risk was found in three studies[17 30 32] and in the curing department of the Akron, Ohio cohort.[20] No excess risks were found in three other studies,[16 24 33] and in the reclaim department of the Akron, Ohio study.[21]

Case-control studies

A threefold excess risk for rubber and plastic workers was found in one[58] out of two available studies.[78]

CANCER OF THE PANCREAS

Cohort studies

Excess risks of cancer of the pancreas ranging from 1.5 to 2.6, were found in four studies,[15 30–32] and in the tyre curing department of the Akron, Ohio plant.[20] Lower excess risks were found in one additional study[17] and in the reclaim department of the Akron, Ohio

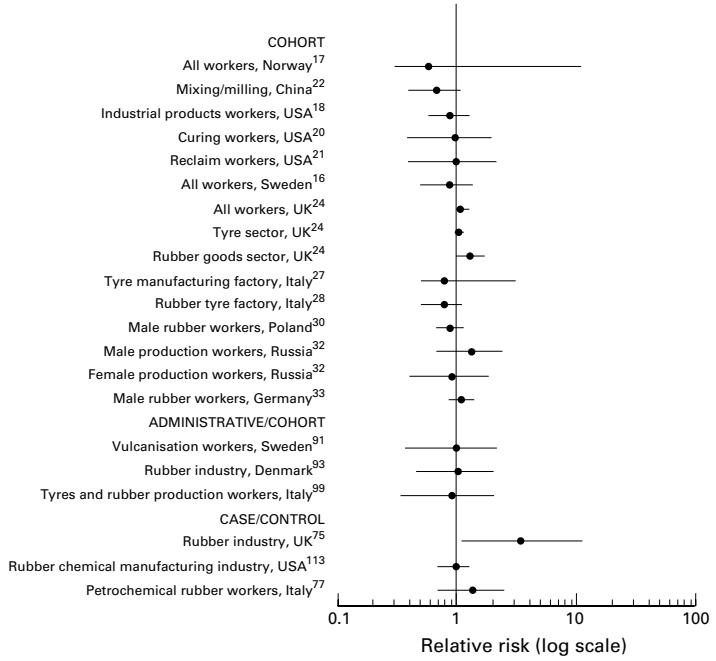

Figure 4 Stomach cancer risk in workers employed in the rubber industry. Odds ratios (95% CIs) for studies including >5 exposed cases.

cohort.[21] No excess risk was found in four cohort studies[24–28 33] and in the industrial products department of the Akron, Ohio cohort.[18]

LIVER CANCER

Cohort studies

A higher than fourfold risk for liver cancer was found in two studies.[15 27] A lower excess risk was found in the BRMA cohort in the United Kingdom (SMR 1.4),[24] whereas no excess was found in four other studies.[22 28 30 33]

Case-control studies

A twofold excess risk for subjects employed in rubber or plastics manufacturing, was found in a population based case-control study in the United States.[58]

CANCER OF THE LARYNX

Figure 5 shows the results of the studies on laryngeal cancer.

Cohort studies

Low or moderate excess risks were found in all seven studies reporting results on laryngeal cancer,[16 24–28 30 32 33] although 95% CIs were wide. The highest risks were found for workers in Russia[32] and Poland.[30]

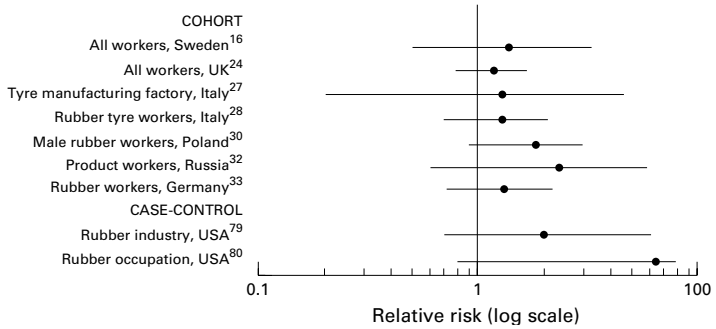

Figure 5 Laryngeal cancer risk in workers employed in the rubber industry. Odds ratios (95% CIs) for studies including >5 exposed cases.

Case-control studies

Two case-control studies in the United States found a high risk among rubber industry workers.[79 80]

NON-MELANOCYTIC SKIN CANCER

Cohort studies

An excess risk was found in three studies[15 16 27 28] but no excess was seen in the remaining four cohort studies that reported results for this cancer.[24 30 32 33]

Case-control studies

Excess risks among workers exposed to rubber stock (OR 2.2) and lubricating oils (OR 6.5) were found in a nested case-control study in rubber industries in Akron Ohio.[39]

BRAIN TUMOURS

Cohort studies

An excess risk was found in five studies.[15 17 27 30 32 34] No excess risk was found in four other studies.[24 28 31 33]

Case-control studies

A higher than twofold excess risk was found in two studies in Canada[85] (OR 9.0), and the United States[86] (OR 3.5). No excess (OR 0.4) was found in a nested case-control study in the Akron, Ohio cohort.[40]

PROSTATE CANCER

Cohort studies

An excess risk was found in four studies[17 27 32 33] and in the industrial products department of the Akron, Ohio cohort.[18] No excess risks were found in three other studies[16 24 30] and in the aerospace and reclaim departments of the Akron, Ohio cohort.[19 21]

Case-control studies

No excess risk was found in two case control studies that reported risk for employment in the rubber industry.[81 82]

KIDNEY CANCER

Cohort studies

A low excess risk not exceeding 1.5 was found in three studies,[28 30 32] and in the reclaim department of the Akron, Ohio cohort.[21] No excess was found in two cohort studies,[16 24] and in the industrial products department of the Akron, Ohio cohort.[18]

Case-control studies

A higher than twofold risk was found in two studies.[83 84]

OTHER CANCERS

An excess risk of thyroid cancer was found in the BRMA cohort (SMR 1.7, 9 deaths)[24] and in an Italian cohort study (SMR 5.0, 1 death)[27]; no excess was found in a study in Russia.[32] Excess risks have been described sporadically both in cohort and in case-control studies for other neoplasms such as cancers of the

nasopharynx,[88] the oropharynx,[89 97] and the uterus,[103] malignant melanoma,[103] and soft tissue sarcoma.[90]

Discussion

A moderate excess risk of cancer of the bladder and the lung and of leukaemia was found in most studies of workers employed in the rubber industry in different regions of the world. A small but consistent excess risk was found for laryngeal cancer. There was an indication of an excess risk of other neoplasms—such as lymphomas and pancreatic and brain tumours—but results were not consistent between studies. There was little evidence of an excess risk of stomach cancer. Detailed exposure information was lacking in nearly all available studies and an evaluation of cancer risk by specific exposures and processes within the rubber industry was, therefore, not possible.

We based our conclusions on the consistency of results across studies and on the magnitude of the reported risks. We did not pay much attention to statistical significance, nor did we attempt to apply techniques of meta-analysis and calculate pooled risk estimators.[114] Firstly, many studies were small and although they identified excess risks, they had little power to detect significant results. For example, in very few studies was the excess risk of leukaemia significant at the conventional α level of 0.05. It is possible, however, that the excess risk of leukaemia is causally related to occupational exposures in this industry, given the recorded widespread exposure to solvents in the past. By contrast, small effects—such as the 10%–20% excess risks for oesophageal and stomach cancer, which in the large BRMA cohort in the United Kingdom were significant—could have resulted from confounding by socioeconomic status. Secondly, the heterogeneity of exposure circumstances within and between plants,[13] differences of occupational and exposure classifications used in the studies, and differences in study design, complicates the calculation of pooled estimators for specific exposures or departments, and makes the calculation of a single summary risk estimate uninformative. Finally, although nearly all cohort studies presented results for cancers of the bladder, lung, stomach, pancreas, and leukaemia and lymphomas, reporting was incomplete for other cancers. Reporting for other sites may have been biased with positive findings overreported even when based on small numbers. A similar argument may hold true for case-control studies and the reporting of risks for employment in the rubber industry.

A moderate excess risk of bladder cancer was found in most of the new studies. This excess risk had been associated in earlier studies with exposure to an antioxidant contaminated with β-naphthylamine,[1] and removal of this agent from rubber plants in the United Kingdom has been shown to prevent the occurrence of further cases of bladder cancer.[5] However, in many recent studies conducted in both developed and developing countries, an excess cancer risk was found among workers with no recorded exposure to β-naphthylamine. This indicates that other agents in this industry may also be associated with the occurrence of bladder cancer among rubber workers. This finding implies that the removal of a single agent from this industry, although important for diminishing the risk in some plants, may not suffice to eliminate the excess risk of bladder cancer found among workers of this industry in several countries.

In the previous IARC evaluation,[1] the excess risk of leukaemia was considered to be real and was attributed to exposure to solvents, particularly benzene. Results from most recent studies tend to confirm this conclusion. The magnitude of the risk varied between studies, with the highest risks found in studies conducted in North America. A variety of solvent mixtures, with or without benzene, have been used in rubber cements, glues, binding, and release agents. As for bladder cancer, these findings suggest that removal of a single agent (benzene) may not eliminate the risk of leukaemia in the entire industry because of widespread exposure to various carcinogens.

Recent studies tend to confirm the presence of a moderate excess risk of lung cancer, and on the whole results are now more consistent than at the time of the IARC evaluation. Relative risks were >50% in many cohorts, indicating that the excesses found are unlikely to be due solely to confounding by smoking[115] or other lifestyle factors.[6]

An excess risk of stomach cancer was identified in earlier studies of workers in the rubber industry, and has been reported in a recent case-control study from the United Kingdom.[75] Cohort studies reported after 1982 either do not confirm the presence of an excess risk of stomach cancer in this industry or suggest the presence of only a slight excess risk. A significant excess risk was found in the largest workers cohort.[24] The risk, however, ranged between 1.1 and 1.3, and is well within the margins of an effect of confounding by socioeconomic status.[116]

Findings for other cancer sites, with the exception of laryngeal cancer, are not consistent between studies, or derive from too few studies. Excess risks found in single studies may be related to specific exposure circumstances occurring in particular rubber plants. One of the most important problems, however, in evaluating findings for other cancer sites, is that reporting may have been incomplete in cohort and case-control studies, with possible preferential reporting of positive findings. The overall findings, therefore, do not provide clear support of excess risks for most of the remaining cancers. The available evidence does not allow an evaluation of the specific agents that may be associated with the increased risk for laryngeal cancer in this industry.

Exposure levels to chemical agents in the rubber industry have decreased in recent years, at least in industrialised countries.[13 14] It is consequently plausible that rates of disease among the workers would have also diminished. Existing epidemiological studies, however, have not shown an elimination of an excess cancer risk. There are some indications that risks are higher

among workers employed in early years and in less developed countries where presumably exposures are less controlled. The few recent studies of workers employed after the 1960s do not have enough power yet to detect potential moderately increased rates of disease. Even these few studies refer to exposure levels in the 1960s which were different both in level and in type than exposures in modern rubber plants. Also, it should be stressed that exposure patterns in industrialised countries may not be representative of rubber plants in newly developed or developing countries. The sparse available data indicate that exposure levels are higher in industries of such countries where many sectors of this industry, such as tyre production, tend to be transferred.[117]

Recommendations and conclusions

Existing studies in the rubber industry have shown the presence of a cancer risk. The potential for diminishing this risk by controlling exposures has also been shown. A common characteristic of existing studies is the absence of detailed exposure assessment and the link between specific exposures and specific risks. New epidemiological studies in this industry should preferably rely on cancer incidence rather than mortality statistics and should provide a detailed evaluation of specific occupational exposures. New studies should also focus on new (or newly identified) risks, such as the possible increase in laryngeal cancer. Biochemical epidemiological techniques should be incorporated both for the evaluation of exposure—for example, measuring aromatic amine haemoglobin or DNA adducts—and of possible interactions between genetics and the environment—for example, examining genetic polymorphisms.[118 119] Their role relative to occupational exposures in workers in this industry has been little evaluated.

In conclusion, findings of epidemiological studies in the rubber industry published after 1982 indicate that there is a moderate increase of the risk of neoplasms of the urinary bladder, lung, larynx, and leukaemia. There was a considerable variation of the risk estimates between studies, but the excess risks were found in many countries and in many different departments indicating that they may be causally related to occupational exposures in this industry. Evidence for other cancer sites, including the stomach, is inconsistent and possibly affected by reporting bias. Examination of new cohorts of workers in the rubber industry, incorporating detailed methods for assessment of exposure and examining various genetic susceptibility markers, may contribute to assessing present risks in this industry and associate these risks with specific exposures.

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Medical editors' trial amnesty

As described in an editorial in the *British Medical Journal*,[1] medical editors of nearly 100 international medical journals are taking action to try to ensure that the results of unpublished randomised controlled trials become available to be included in systematic reviews. This could have important benefits for patient care.

Any reader who would like to take up this opportunity to register the results of a trial that did not getpublished can do so on a special *unreported trial registration form*. Copies are available from the *Occupationaland Environmental Medicine* editorial office.

I do not expect that many *Occupational and Environmental Medicine* readers will need to take up this offer, given the nature of our field, but perhaps I will be proved wrong.

ANNE COCKCROFT
Editor

1 R Smith, I Roberts. An amnesty for unpublished trials. *BMJ* 1997;**315**:622.