DRAFT CC/04/13

COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD CONSUMER PRODUCTS AND THE ENVIRONMENT

REVIEW OF PROSTATE CANCER: Incidence of prostate cancer mortality within the rubber industry

Cover paper.

Introduction

1. Members will recall from the 1 April 2004 COC meeting that HSE asked for the COC evaluation of the evidence regarding prostate cancer within the rubber industry. The appended paper has been prepared by the DH Toxicology Unit (Annex 1).

2. A number of relevant papers have been appended as Annex 2.

   McMichael AJ et al. JOM, vol 18, 178-185, 1976
   Sorahan T et al. Brit J Ind Med, vol 43, 363-373, 1986.
   Bernardinelli R et al. Brit J Ind Med, vol 44, 187-191, 1987.
   Straif K et al. Occup Environ Med, vol 57, 180-187, 2000.
   Andjelkovich D et al. JOM, vol 19, 397-405, 1977.

3. Do members agree with the approach taken in the review paper and the overall conclusion reached in the DH Tox Unit review (Annex 1), that there is no convincing evidence of an increased risk of PC in rubber workers as a whole.

4. An overall draft conclusion has been prepared for inclusion in the statement. Do Members agree with the text?

   "The further review undertaken by the DH Toxicology Unit at the request of the COC identified epidemiological studies undertaken at rubber manufacturing plants in the U.S.A., Europe and the U.K. as well as two studies where the location of the rubber manufacturing plant was not reported. Overall there was no convincing evidence to associate employment in the rubber industry with prostate cancer. A number of the research groups reported investigations into the association between employment in particular departments and prostate cancer. The clearest evidence for such an association came from studies of rubber plants in the U.S.A. regarding compounding and mixing but no definite conclusions could be drawn. There was no convincing evidence to associate prostate cancer with any particular chemical exposure at rubber plants.

   The evidence is consistent with the view that overall, there is no convincing evidence of an increased risk of PC in rubber workers as a whole."

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Secretariat June 2004

Incidence of prostate cancer mortality within the rubber industry

Introduction

Prostate cancer (PC) is estimated to be the third most common cancer in men with 27149 cases being diagnosed in 2000, and 9937 mortalities occurring in 2002 (Cancer Research UK). The disease is prevalent in the elderly, with around three-quarters of cases occurring in men aged ≥ 65 years, although rates do decline > 80 years of age. The aetiology of PC is unclear as risk factors have yet to be fully established, but it has been suggested that age, family history and ethnicity may contribute, as well as hormonal patterns and dietary factors.

Historically there has been an interest in the link between the rubber industry and adverse health effects due to the use of a diverse range of organic and inorganic compounds in rubber manufacturing and workers being faced with a variety of hazards in the various

phases of the complex manufacturing process (Bernardinelli *et al*., 1987; Mancuso *et al.*, 1968; McMichael *et al.*, 1976a). Moreover, continuous introduction of new chemicals, due to the development of new rubber and rubber related products poses great concern (Mancuso *et al.*, 1968).

Specific jobs within a rubber plant may be linked with excess mortality (McMichael *et al.*, 1976b). However, the exposure conditions in the rubber industry are complex and highly variable between work sites and plants, and over time, making it difficult to attribute the excess cancer incidence to specific exposures (Weiland *et al.*, 1996).

Among the list of chemicals used to date or those that have been previously used are some proven human chemical carcinogens such as β-naphthylamine, 4-aminediphenol, benzidine, benzene, mineral oil, soot, vinyl choride and asbestos, and probable human carcinogens such as styrene, acrylonitrile, N-phenol-β-naphthylamine, nitrosamines, formaldehyde and carbon tetrachloride (McMichael *et al*., 1976b; Wilczynska *et al.*, 2001). In addition, due to the high temperatures involved in several of the processes, many chemical reaction by-products are produced with unknown carcinogenic potential (McMichael *et al.*, 1976a; McMichael *et al.*, 1976b).

Health effects of employment in the rubber industry have been the subject of a number of epidemiology studies (Wilczynska *et al.*, 2001). Early reports showed an elevated proportion of deaths due to cancer, including respiratory, genitourinary and central nervous system cancer (McMichael *et al.*, 1976a). In 1982 an IARC working group published an evaluation of the carcinogenic risks in the rubber industry. For lung and stomach cancer, the report concluded that there was sufficient evidence for an excess occurrence in rubber workers and limited evidence to support a causal association with occupational exposure (IARC, 1982). In addition, in 1987, IARC recognised that there was an association between working in the rubber industry and excess bladder cancer, due to exposure to aromatic amines, and also excess leukaemia, attributed to exposure to benzene (IARC, 1987). However, an association between rubber workers and PC has not been proven. Associations between PC mortality and employment in the US rubber industry have been reported, both in workers stationed at specific work areas as well as those in different

facilities (Goldsmith *et al.*, 1980). In contrast, other studies have reported a deficit in PC mortality (McMichael *et al*., 1974; Sorahan *et al*., 1986; Sorahan *et al*., 1989).

At its April 2004 meeting the COC asked that a review be prepared of the evidence for an association between PC and working in the rubber industry. This report attempts to identify specific job categories or chemical exposures that may be associated with such an increased incidence of PC. The report identifies studies in terms of the geographical location of plant, the risk of PC in different occupational categories and following different chemical exposures.

Risk of PC in rubber plants in different locations

Twelve reports have been retrieved regarding rubber plants, four from US and eight from Europe.

US plants

Within the US, all four studies regarding PC mortality in employees in the rubber industry have been carried out in rubber plants located in Akron.

An epidemiologic study of mortality within a cohort of rubber workers employed in a tyre manufacturing plant in Akron was carried out by McMichael and co-workers, using an historical prospective design (McMichael *et al.*, 1974). The cohort comprised 6678 rubber plant employees, who were aged between 40 and 84. All workers were either active or retired in 1964. The cohort was divided into sub-cohorts; an active age range (40-64 years of age), retired age range (65-84) or full age range (40-84 years of age) for which the person-years at risk were 31548, 19798.5 and 51346.5 respectively. Female employees, who comprised approximately 10% of the cohort were not included in the study. Information regarding the cohort was obtained from company records, pensions and death certificates. All workers were followed for a nine-year period during which time 1783 life insurance death claims were paid on behalf of deaths within the cohort. These represented the total mortality within the cohort during 1964-1972. Death certificates were obtained for all but nine (0.5%) of these 1783 deaths, from which a nosologist coded information regarding cause of death by using the Eighth Revision of the International Classification of Diseases. Controls were made up of the US male population, regardless of ethnic

background. Later examination of the proportion of black workers (14%) suggested that the racial composition of the cohort was similar to that of the national male population within the same age range. Results from the study showed that mortality from malignant neoplasms of the prostate was higher, although not significantly, than expected for the full age range (40-64 years old, observed (O)=6, expected (E)=4.1, standardised mortality ratio (SMR)=147) and significantly higher in the active age range (40-84 years old, O=49, E=34.4, SMR=142) (McMichael *et al.*, 1974).

In a similar study, Andjelkovic and colleagues carried out an historic prospective study in a rubber manufacturing plant in Akron, with the objective of exploring if mortality in rubber workers exceeded that in other industries or in the general public (Andjelkovic *et al.*, 1976). The cohort consisted of 8938 people (94% white) over the age of 40 in 1964, who were active, or living retired hourly workers. Two thousand seventy three (28%) workers died during the ten-year follow-up period, between 1964 and 1973. Approximately a third of all participants belonged to each age group, namely 40-54, 55-64 and 65-84, although the authors used the age groups 40-64, 65-84 and 40-84 for analysis. 98.4% of all workers included had worked in the rubber industry for at least ten or more years. Data were collected from company and union records and from death certificates and a nosologist coded the causes of death according to the Eighth Revision of the International Classification of Diseases. Retirement information was also obtained, including age of retirement and date. The standard population used to calculate the SMRs consisted of the US male population of comparable age, sex and race, although the authors acknowledged that this was not the most appropriate control group. In the study, an excess mortality rate from PC, although not statistically significant, was observed for the 40-64 (SMR=148), 65-84 (SMR=105) and 40-84 (SMR=109) age ranges. When considering only retired workers, a significant excess risk for PC was observed in the younger age group (40-64 years old, SMR=278), whereas the other age groups were comparable to the active workers (65-84 years old, SMR=105; 40-84 years old, SMR=111) (Andjelkovic *et al.*, 1976).

In order to determine to what extent mortality of short-term workers reflects that of long-term employees, Delzell and colleagues studied subjects that worked at a rubber manufacturing company in Akron since the late 1800s (Delzell and Monson, 1981). In this

study, the cohort consisted of 29087 employees. Information such as name, demographic characteristics and employment dates were obtained from company records, and union records supplied data regarding sequential departmental changes. Five study groups were defined on the basis of employment category, race and sex, namely 15643 white male union members, 1184 non-white male union members, 4200 female union members, 4683 salaried males and 3377 salaried females. There were approximately 441985 person-years of observation for white male union members, 28729 for non-white male union workers, and 110987 for salaried males. Average period of follow-up was 28 years for white male union workers and 24 years for non-white male union members and salaried males. Employees were classified as salaried if they had no record of employment in production jobs. The company censuses in 1974 and 1979 identified 4470 active employees, of undetermined sex, among the 21510 male cohort and follow-up to ascertain mortality began in 1940 and continued until 1978. The company provided death certificates for the 9388 deceased employees (95.3%), although the authors did not state the deceased sex. The underlying cause of death was coded according to the Seventh Revision of the International Classification of Diseases. The US general population acted as a control group. Data from the study showed that no significant excesses were observed for PC (1940-1974, O=95, SMR=103; 1974-1978, O=26, SMR=101; 1940-1978, O=121, SMR=102, 95% CI=85-122) (Delzell and Monson, 1981).

A population-based case-control study was carried out by Elghany and colleagues to investigate associations between PC and work history in a rubber plant in Utah (Elghany *et al.*, 1990). Three hundred fifty eight white men with newly identified PC aged between 45 and 74 years old were included in the study, and 679 males from the Utah population were considered as controls. Eligible cases diagnosed with PC had histological confirmation, which was categorised by the Ninth Revision of the International Classification of Disease. In addition, the Utah Cancer Registry was used to complete case ascertainment. Trained interviewers questioned all participants using a standard questionnaire and collected information regarding occupational history, including industries, occupations and exposures. The longest and most recent industry and occupational task and duration of employment and/or exposure were also ascertained. Duration of employment or exposure was subdivided into workers exposed for <20 years, > 20 years or those never exposed. In

addition, participants were grouped into two age groups, <67 years old or >67 years old. Data show that employment in the rubber industry appeared to be protective against all tumours, including PC (cases, n=0, controls, n=8, OR not calculated) (Elghany *et al.*, 1990).

Conclusion: risk of PC in US rubber plants

There is no convincing evidence for an association between PC mortality and employment in the US rubber industry.

German plants

One study was retrieved that investigated the incidence of PC mortality in German rubber plants.

A cohort of 11663 German men was followed up for mortality from 1981 to 1991 (Weiland *et al.*, 1996). Cohort members were active (7536) or retired (4127) at the beginning of the study. All workers had been employed for at least one year in a German rubber plant either producing tyres or rubber goods. Men >85 years old at the beginning of follow up or those that had not been employed for one year were excluded from the study. Work histories of the cohort members (99.7%) were identified through personnel files from the rubber plants and included information regarding year of employment and years since employment. For cohort members that had died (2719), death certificates were obtained for 2631 (96.8%) and causes of death were coded according to the Ninth Revision of the International Classification of Diseases by a trained nosologist. The reference group consisted of the male population of Western Germany. Slightly increased mortality, (although not statistically significant) in the active workers and total worker groups, was observed for PC (active workers, O=63, SMR=110, 95% confidence interval (CI)=85-141; retired workers, O=8, SMR=92, 95% CI=40-182; total workers, O=71, SMR=108, 95% CI=84-136). When considering the year of employment, a non-significant excess risk was observed in retired workers (O=41, SMR=131, 95% CI=94-198) and total workers (O=42, SMR=128, 95% CI=92-173) employed < 1950. Active employees employed between 1950-1959 also showed a non-significant excess risk (O=6, SMR=133, 95% CI=49-298) and retired workers employed >1960 (O=0, SMR=111, 95% CI=51-212). Analysis of years

since hire showed that no employees working <10 years were diagnosed with PC, and only 2 retired (O=2, SMR=149, 95% CI=18-537) and 2 of the total workers (O=2, SMR=109, 95% CI=13-392) employed for 10-19 years had PC. Higher numbers of PC were observed in the group of workers employed for > 20 years with a slight excess in the retired and total groups (active workers, O=8, SMR=99, 95% CI=42-194; retired workers O=60, SMR=109, 95% CI=83-140; total workers, O=68, SMR=107, 95% CI=83-136), although again, none were statistically significant (Weiland *et al.*, 1996).

Conclusion: risk of PC in German rubber plants

This study did not provide any convincing evidence to suggest an increase risk of PC in German rubber workers.

UK plants

Four studies were retrieved that investigated the incidence of PC mortality in the British rubber industry. Within the UK, both studies carried out by Sorahan have been carried out using the same cohort from 13 participating rubber factories.

Sorahan and co-workers carried out a population-based case-control study to investigate the cancer mortality in the British rubber industry (Sorahan *et al.*, 1986). All male workers (36445) employed in any of the 13 participating plants during 1946-1960 were included in the study and all participants had worked continuously in the plant for a minimum of one year. Detailed job histories between 1976 and 1980 were recorded for each worker, which were checked with the National Health Service Central Register of the Health and Safety Executive. The mortality of the cohort was compared to that for the general population of England and Wales, or Scotland. Data from the study show a statistically significant decrease in PC (O=59, E=79.7, SMR=74). Due to this observed decrease, no further analyses were undertaken (Sorahan *et al.*, 1986).

A second similar study was carried out by Sorahan in which job histories were recorded between 1976-1985. Again, a statistically significant deficit for PC was observed (O=91, E=128.2, SMR=71) (Sorahan *et al.*, 1989).

Straughan and Sorahan carried out a later prospective cohort study to investigate if the improved working conditions, introduced into the British rubber industry in recent decades, are paralleled with a decrease in cancer, although the main focus of the report was towards lung and stomach cancer (Straughan and Sorahan, 2000). The second aim was to report findings for other cancers in an early follow-up period. The cohort consisted of 9031 male and females workers. All subjects had been employed for at least 12 months and were first employed at one of the 42 rubber factories in the UK between 1982-1991. Data were obtained from the plants including work histories and smoking history during the 10-year period. The Office for National Statistics provided vital status data up until 1998 and cancer registrations between 1983-1994. Mortality data were available for the period 1983-1998. At the end of the study, 8329 (96.3%) subjects were alive, 136 (1%) were dead, 27 (0.3%) had emigrated and 159 (1.8%) were untraced. For deceased subjects, the underlying cause of death was coded according to the Ninth Revision of the International Classification of Diseases. The mortality and incidence of cancer within the cohort were compared to expected values in England and Wales calculated by period, age and sex. Data show a decrease in PC registration was reported during 1983-1994 (O=1, Exp=1.83, (standardised registration ratio SRR)=55) and no cases of PC mortality were observed during 1983-1998 (O=0, E=1.76, SMR=0) (Straughan and Sorahan, 2000).

A study carried out by the HSE investigated the mortality in the British rubber industry. The cohort comprised 40867 male workers that had been employed in one of the 381 rubber plants in 1967. All participants were >35 years and had worked in the rubber industry for at least one year. The follow-up period was from 1967-1976, during which time 5773 members of the cohort died. Data on the cohort were obtained from the National Health Service Central Registers for England, Wales and Scotland. Copies of death certificates were obtained and the underlying cause of death coded according to the Eight Revision of the International Classification of Diseases. All members of the cohort were placed into one of three groups. Group A, started work before 1950 in a factory that used antioxidants (n=12779); group B, started work after 1950 in a factory that used antioxidants (n=18118); group C, worked in factories that had never used the antioxidants (n=9970). Factories using antioxidants were identified from a survey by HM Factory Inspectorate in 1965. The number of person years was calculated for those who died, for

those who emigrated and for survivors until the end of the follow-up period in 1976. The numbers of expected deaths for the whole industry were calculated using morality rates for England and Wales and compared to those obtained using social class specific mortality rates. Mortality data were presented for the whole industry and also for individual departments. This study reported that in three of the 381 rubber plants, the SMRs for PC were significantly increased (authors do not present data). Five out of the nine deaths due to PC occurred in men who had worked in factories classified as group A. When the authors excluded these cases from the study, results were no longer significant (O=55, E=55.8, SMR=99). Slight excess risks of PC were seen in various industry sectors, including tyres (O=21, E=20, SMR=105), cables and electrical good (O=5, E=3.6, SMR=139), footwear and footwear supplies (O=3, E=2.1, SMR=143), sponge rubber and rubber with plastic crepe rubber (O=2, E=1.8, SMR=110), mouldings, motor accessories and mechanicals (O=17, E=14.3, SMR=119). Deficits for PC were seen in employees working in sectors producing clothing, rubberised textiles, hair and carpeting (O=2, E=3.1, SMR=63), belting, hose and rubber with asbestos flooring (O=4, E=5.4, SMR=74) and surgical and medical supplies (O=1, E=1.1, SMR=89). No PC mortalities were observed in workers employed in the production of tyre remoulds and retreads, adhesives, rubber solutions and sealing compounds, printing supplies, ebonite and vulcanite and other rubber goods.

Conclusion: risk of PC in UK rubber plants

The work of Sorahan demonstrates a decrease in the incidence of PC in British rubber plant workers. The additional study by the HSE does not provide convincing evidence of a significant association between PC and workers in the British rubber industry.

Italian plants

One study was retrieved regarding the incidence of PC in an Italian rubber plant.

An attempt was made by Bernardinelli to identify any occupational cancer hazard that might affect men working in the rubber industry in Italy (Bernardinelli *et al.,* 1987). The cohort used, comprised all 5068 male workers employed by an Italian rubber factory from 1962 to 1972, and was followed up until 1983. There were 6560 person years at risk for the 15-24 age group, 31566 for 25-34, 23697 for 35-44, 6494 for 45-54, 916 for >55 and

69233 for all ages. Personal data and information on employment, including dates that employment commenced and terminated, place of work within the factory and reason for termination was obtained from company records. The cohort was subdivided into two groups, namely office and non-office workers. Because of the small number of office workers, they were excluded from the analysis. Of the remaining 4917 non-office male participants, 3784 were active employees, 78 were retired, 110 had died and 1096 had left employment. All subjects that had left employment were traced, with the exception of four that had emigrated. Death certificates were obtained for all but two of those who had died and a nosologist coded the cause of death according to the Eighth Revision of the International Classification of Diseases. A reference population was selected that was closest to the cohort with respect to living habits and environmental exposure (authors did not define what environmental exposures have been included and no further details were given). Results obtained from the study showed a significant increased risk of PC (O=2, SMR=518) (Bernardinelli *et al.*, 1987).

Conclusion: risk of PC in Italian rubber plants

This study provides some evidence of a small but significant association between PC and workers in the Italian rubber industry. However because of the very small number of cases and the limited details of the reference (control) population, no definite conclusions can be drawn.

Russian plants

One study was retrieved regarding the incidence of PC in a Russian rubber plant.

Solinova and colleagues assess the mortality and cancer incidence of workers in a Moscow rubber plant producing rubber footwear and other rubber products (Solionova and Smulevich, 1993). The cohort consisted of 3670 workers (1178 men and 2492 women) who had been employed for at least ten years between 1979 and 1983. Of these, 2090 were still employed, 968 were retired, 121 had died and 443 had left the plant. A total of 10302 person years were included in the study. The follow- up period was between 1979-1988. During the follow-up period, 195 male deaths were recorded, of which 66 were due to cancer, the total number of cancer cases being 84. Information about the cohort was obtained from central and local registry offices, records from outpatient cancer clinics and

pathology departments. The cause of death was determined via registry offices and for all subjects that had cancer stated on the death certificate, medical history and autopsy details were obtained from the hospital in which they were treated and coded according to the Ninth Revision of the International Classification of Diseases. Job histories of each employee were obtained from the plant. Subjects were categorised as production or non-production workers. The authors further categorised the exposed workers as workers in the preparatory shop, in vulcanisation or in other areas, although data for PC were not presented in such categories. The SIR or SMR was calculated using the general population of Moscow between 1979-1988 as the reference population. Data show a non-significant deficit in PC mortality (O=1, E=1.7, SMR=58, 95% CI=1-323) among all male workers, and a non-significant excess risk of PC in production workers (O=3, E=1.2, SIR-247), non-production workers (O=1, E=0.7, SIR=129) and in the total male cohort (O=4, E=1.9, SIR=202) (Solionova and Smulevich, 1993).

Conclusion: risk of PC in Russian rubber plants

This study did not provide any convincing evidence to suggest an increase risk of PC in Russian rubber workers.

Swedish plants

One study was retrieved regarding the incidence of PC in a Swedish rubber plant.

An initial retrospective study from two Swedish rubber manufacturing industries was initiated in the 1970s and had a follow-up period from 1961-1977. A later study, carried out by Gustavsson and co-workers extended the follow-up period to cover the time period 1952-1981 (Gustavsson *et al.*, 1986). The original cohort comprised 13114 subjects, 10622 were exposed production workers and 2492 were unexposed office workers that acted as an internal reference group. After applying several exclusion criteria, such as excluding workers employed for < 1 year and those that had left work before 1952 due to follow-up being difficult, the cohort consisted of 12212 subjects (7932 men and 4280 women). The exposed subjects had worked in the weighing and mixing departments and were categorised into two groups; subgroup 1 had a latency requirement of 10 years and subgroup 2 was first employed before 1951, was exposed > 5 years and had a latency

requirement of 20 years. The total person years at risk in the exposed group was 179894. Data on the living population were obtained from the Swedish National Central Bureau of Statistics and cancer cases were identified from 1959-1980 from the National Cancer Registry. The expected values of cancer were calculated by using national statistics for mortality and cancer incidence. Within the exposed cohort there was a non-significant decrease in PC mortality (O=13, E=16.95, SMR=77, 95% CI=10-131) and incidence of PC (O=34, E=41.29, SMR=82, 95% CI=57-115). Mortality due to PC in workers employed in the weighing and mixing departments was lower than expected in both subgroups (subgroup 1; O=2, SMR=71; subgroup 2, O=0, SMR=0) as was the incidence of PC (subgroup 1; O=5, SMR=72; subgroup 2, O=2, SMR=66) (Gustavsson *et al.*, 1986).

Conclusion: risk of PC in Swedish rubber plants

Slight decreases in mortality and incidence of PC were observed in Swedish rubber workers, although the effects observed were not statistically significant.

Norwegian plants

One study was retrieved regarding the incidence of PC in a Norwegian rubber plant.

Norseth and co-workers investigated the cancer incidence in a rubber plant located in rural Norway (Norseth *et al.*, 1983). The plant supplied lists of all employees working in the plant in 1940 or who were employed after this date. All employees who were still alive in 1953 were included in the study and were followed until 1978. The study focussed on male employees, because females changed their names at marriage and hence were difficult to trace. The cohort comprised 3179 workers, 398 workers were employed after 1970, 317 workers were employed < 18 months, 13 workers had died before 1953 and 3 were untraceable. The authors provided no further information about the study. The numbers of cases of PC were increased compared to the expected numbers (O=23, E=20.87) (Norseth *et al.*, 1983), although the authors did not state whether this referred to PC mortality or incidence.

Conclusion: risk of PC in Norwegian rubber plants

This study did not provide convincing evidence of an increased risk of PC in Norwegian rubber plant workers.

Overall conclusion: risk of PC due to plant location

Overall, the evidence does not suggest that rubber workers are at an increased risk of PC.

Job categories increasing risk of PC

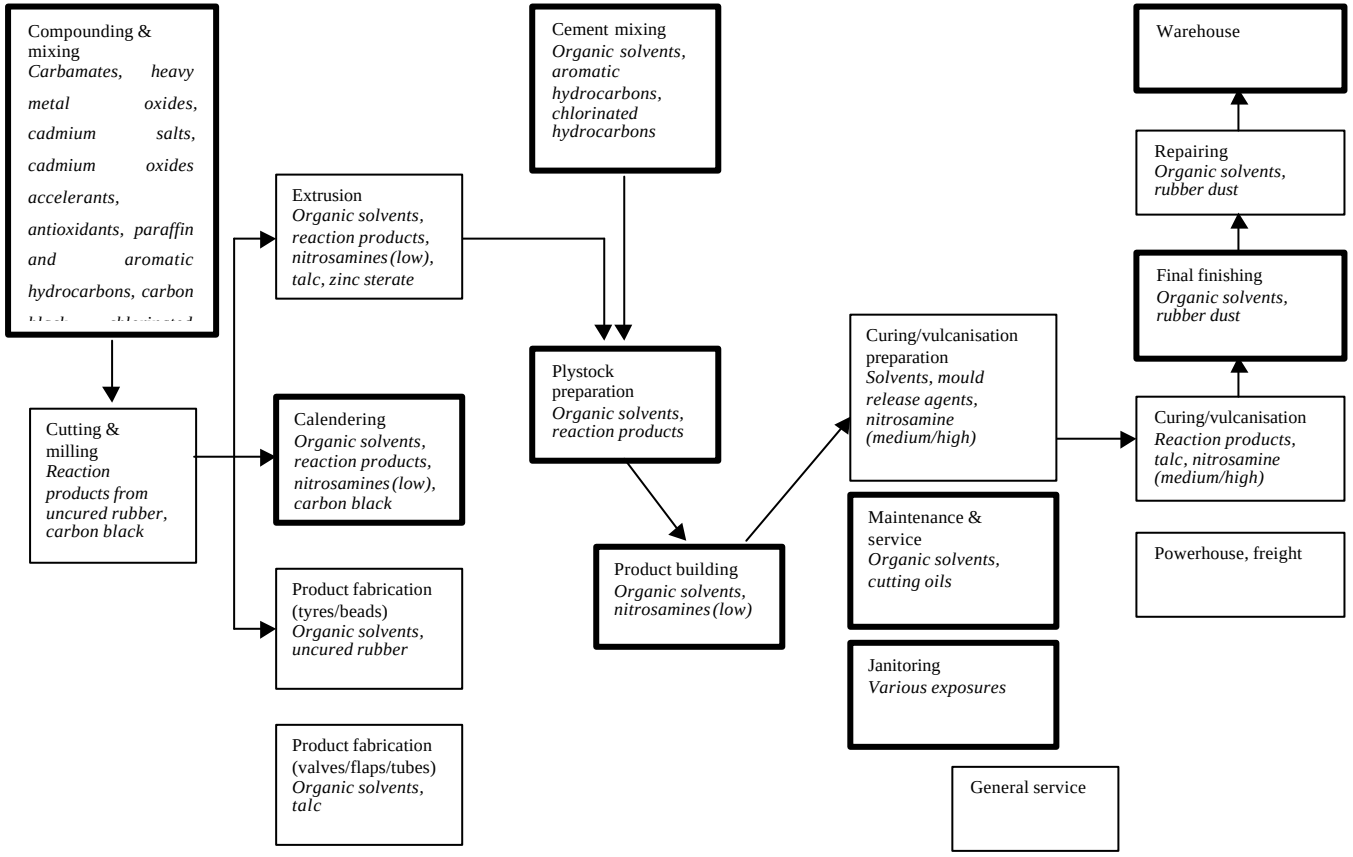
A diagrammatic representation of general rubber production and potential chemical exposures in each area is shown in figure 1. Nine studies have been retrieved that focussed on the associations between excess mortality of PC and specific jobs within the rubber industry. Five studies were carried out in US, one in Germany, one in Poland and two in unspecified locations.

US plants

McMichael and co-workers carried out a second study with the aim to determine the cancer mortality in US rubber workers and attempted to identify specific jobs, and where possible specific chemicals, that were associated with an increased risk of caner mortality (McMichael *et al.*, 1976a). Four cohorts of male workers were identified at the main tyre-manufacturing plant in each of the four rubber companies, three of which were located in Akron and one in Wisconsin. All workers were either active (40-64 years of age) or retired (65-84 years of age) in 1964. Of the total of 19803 workers, 98% had worked in the rubber industry for the previous ten years, and the average length of employment was 25-29 years. Data were obtained and deaths were classified as with the previous study, during a ten-year follow-up period. The US male population acted as controls, although the authors stated that use of this standard population introduces an underestimation of mortality, because an active industrial workforce, not exposed to work-related health hazards is normally healthier than a similarly aged sample of the general population. In examining the association between specific cancers and work exposures, detailed work histories were obtained from the companies, for individual workers. Jobs were classified according to type of materials handled and/or production stage. The preliminary analysis carried out in one of the plants was based on the comparison of work-histories between each cause-of-

death group and an age-stratified random sample comprising 23% of the cohort. Each case group was compared to the cohort for differences in the proportion that had spent two or more years in each job category. Data showed a slight excess of PC mortality in the active (40-65 years old) age group (SMR=138) and in the retired (65-84 years old) age group (SMR=116), the total SMR of both groups being 119. No data for 95% CI were presented. Few associations were apparent for PC apart from compounding and mixing, cement mixing, janitoring and trucking (general service), for which 56 cases of PC mortality were observed (McMichael *et al.,* 1976a).

Figure 1. Diagrammatic representation of general rubber production and potential chemical exposures in each area. The diagram was adapted from (Andjelkovic *et al.*, 1977; McMichael *et al.*, 1976a; McMichael *et al.*, 1976b). Most rubber plants consist of the same or similar departments, albeit with minor modifications.
Boxes in bold signify areas in which workers have been shown to have an increased risk of PC in different studies.



As a continuation of the previously mentioned studies, McMichael and co-workers focussed on the association between excess mortality and specific jobs within the same rubber plant. The cause of death analysed in this study i.e. PC, was chosen due to it being observed to be in excess in the previous studies, and the cases were selected for inclusion into the study derived from deaths in the ten-year period between 1964-1973(McMichael *et al.*, 1976b). Of the 1983 identified deaths, 38% were aged 40-54, 30% were aged 55-64, and 32% were aged 65-84. Of these, 48% of workers began work in the plant at least 25 years before 1964, and all but 1% had worked for at least 10 years by 1964.

An equivalent mortality analysis in a smaller cohort was also carried out in 1339 male rubber workers during 1964-1972, from another tyre manufacturing plant in Akron. Detailed work histories including exposure experience were obtained from the plant personnel office for each worker. Due to the many different jobs within the plant, a two-tier job classification system was developed. Jobs were grouped into occupational titled groups (OTGs) and occupational titles (OTs). The study design used in this study required work histories from only approximately a quarter of the study population. This design enabled each case group i.e. PC, to be compared to a sample of the total study population to identify differences in work histories such as frequency and duration of exposure. Frequency and duration of employment (referred to as exposure rates by the authors) were calculated for each subject. In each case group, they were age-adjusted to the age-distribution of the population sample to ensure comparability of the adjusted rates in each case group. When analysing exposure rates, cumulative exposures of less than two years were excluded from the analysis and only deaths occurring within a specific time period were included. Two minimum exposure durations (two and five years during 1950-1960) were used to identify a dose-relationship. If differences were identified from this analysis, an estimate of the risk ratio (RR) associated with the particular job was then made. Data show that out of the total 1983 cohort, 53 cases of PC were observed (SMR=140). Few positive associations were made between PC and job type. For compounding and mixing or cement mixing, ratios of the age-adjusted OTG-exposure rates for exposure >2 or >5 years were slightly increased (relative risk (RR)=1.2 or 1.5, respectively, age standardised risk ratio (RR_{as}) for death=1.6, 99.9% CI=1.2-2.3). For calendaring and plystock handling, RR=1.6 or 2.1, respectively (RR_{as}=2.4, 99.9% CI=1.9-3.3) and for salary, RR=3.8 or 2.8, respectively, RR_{as}=3.5, 99.9% CI=2.8-4.6) (McMichael *et al.*, 1976b).

As a follow-up study from McMichael in 1974 and 1976, Goldsmith and colleagues further elucidated the relationship between PC mortality and employment history in the rubber and tyre industry (Goldsmith *et al.*, 1980). The cohort used was comprised of 88 active or retired hourly rubber workers, at least 40 years old by 1964 and who died between 1964 and 1975. Two hundred fifty eight controls were taken from the same cohort and were matched according to age, race and year of employment. In general, three controls were obtained per case, with some exceptions. Cases were ascertained by death certificates obtained from the company's life insurance carrier. Individual work histories were coded according to the occupational coding scheme as well as demographic information and cause of death. Occupational titles were grouped into occupational title groups, which there then ranked according to estimated exposures. The data obtained show that in 75% of cases, PC was classified as the underlying cause of death. For the remaining 25%, it was noted as 'a significant condition'. Workers employed in batch preparation >1 month had a significantly increased risk of PC ($P<0.025$, n=17, OR=2.8, $\chi^2=6.50$) as well as those employed for >24 months ($P<0.025$, n=14, OR=2.8, $\chi^2=5.75$) and >60 months ($P<0.025$, n=11, OR=3.0, $\chi^2=5.34$). Workers employed in salary >1 month (n=13, OR=2.8, $\chi^2=5.41$) and >24 months (n=7, OR=2.0, $\chi^2=1.44$) also showed elevated ORs. Odds ratios were not calculated for workers exposed for >60 months as there were less than five exposed cases. When matched analysis was repeated for black and white workers separately, in batch preparation, significant OR were recorded for whites at exposures >1 and >24 months (>1 month, n=9, OR=3.2, $\chi^2=5.83$; >24 months, n=7, OR=3.5, $\chi^2=5.77$). Service to batch preparation showed a significant increase at exposures >60 months (n=5, OR=4, $\chi^2=4.05$) only in black workers. These work areas make up the compounding and mixing sections used in other studies. Data for 95% CI were not presented (Goldsmith *et al.*, 1980). The authors suggest that the consistent elevation of risk for batch preparation and the statistically significant OR of approximately 3, are unlikely to be chance events, even though no dose-response relationship was evident.

The mortality among a cohort of white male rubber workers in Akron was studied by Monson and Nakano to investigate the potential risk of cancer in specific work areas (Monson and Nakano, 1976a). In 1971 when the study was initiated, of the 13571

participants, 2610 were active employees, 2988 were retired, 4164 had terminated employment and 3809 had died. Among the terminated employees, 3694 worked <15 years, 268 worked 15-24 years and 202 worked >25 years and 739 had died during the follow up period. Out of the 2988 former retired workers, 511 died during the follow-up period. Follow-up of active and retired employees was continued until 1974. Of the active workers, 1561 were still active after this follow-up period, 20 had died, 508 had retired and most of the remaining workers had been made redundant. Death certificates were obtained for most of the 5079 deceased workers and a trained nosologist coded the cause of death according to the Seventh Revision of the International Classification of Diseases. Data, including age, sex, date and age of first employment at the plant, date of termination, last department worked and reason for termination were collected. The 271 departments within the rubber industry were organised into seven divisions, and sectional groupings, within the divisions, were made of similar departments. The employees departmental work experience was categorised as 'ever' and 'usual', depending on whether they had ever worked in the particular department or whether they had been employed for the longest period in the area. The expected numbers of cause-specific deaths were calculated using death rates for Ohio males, which were similar to those obtained for the US general male population. The data show that there was an overall decrease in the incidence of PC (O=82, E=89, SMR=92). However, when taking into account the different work areas, employees usually working in the miscellaneous tyre area had an increased risk of PC (O=12, E=8.8, SMR=140). 95% CI data were not presented (Monson and Nakano, 1976a).

As a follow-up from the previous study, Monson and co-workers analysed data from the Akron rubber plant, taking into consideration more details regarding work experience (Monson and Fine, 1978). Thirteen thousand five hundred seventy white, male union members, who had worked for at least 5 years prior to 1971 were included into the study and the potential follow-up period was between 1940 and 1976. In the original report (Monson and Nakano, 1976a) cases were considered to have cancer only if it was the underlying cause of death. The criteria were extended in this study and incorporated cases that had cancer listed on the death certificate although not as the underlying cause of death, and cases that were identified on the tumour register in local hospitals. Diagnosis of cancer was made initially from the death certificates, or from the hospital tumour registries. US

white males were used as a control group. No precise data were available from either the company or union regarding the work experience of the workers. Data regarding the department in which the employees worked were obtained from union files, therefore the duration of employment in each department was known and the actual year of entry could be estimated. The employees departmental work experience was defined as the time the worker was employed in various departments. Within the rubber plant, two apparently unrelated departments, namely material conservation (n=28, O=4, E=0.28, RR=7.6) and final finish (n=88, O=4, E=1.2, RR=2.4), were identified in which four men, who had worked for at least 25 years, died from PC. Excess incidence of PC was also observed in workers employed in machine maintenance, with the greatest excess being observed in those working for relatively short periods of time (n=4.2, O=1, E=2, RR=2.1). 95% CI data were not presented (Monson and Fine, 1978).

Conclusion: risk of PC due to occupational title in US rubber plants

Workers employed in compounding and mixing (Andjelkovic *et al.*, 1977; Goldsmith *et al*., 1980; McMichael *et al.*, 1976a), cement mixing (McMichael *et al.*, 1976a), janitoring and trucking (Andjelkovic *et al.*, 1977; McMichael *et al.*, 1976b), calendaring and plystock handling (McMichael *et al*., 1976b), salary (Goldsmith *et al*., 1980), miscellaneous tyre area (Monson and Nakano, 1976b), material conservation and final finish (Monson and Fine, 1978) and maintenance (Monson and Fine, 1978) have all been reported to have a slightly increased risk of PC. However, the number of cases involved in each category was small and there was a lack of consistency between studies. Some of the authors concluded that the excess cases of PC were not likely to be caused by a common exposure, as no apparent link existed among the departments regarding exposures. The variation in job categories with reported evidence of association with PC may also reflect the different approaches to accessing and analysing work histories between the various studies.

German plants

Straif and co-workers investigated mortality among male rubber plant workers in Germany (Straif *et al.*, 1998). A cohort of 11633 male German workers was followed from 1981 until 1991. The workers were classified as active (7536) or retired (4127) in 1981 and had worked in the rubber plants for at least one year. Work histories were obtained and

classified into six categories; preparation of materials, production of technical rubber goods, production of tyres, storage and dispatch, general service and others. The general population of Germany acted as a reference. Data obtained show that mortality from PC was increased, although not significantly, in workers employed in maintenance and general service (O=27, SMR=152, 95% CI=99-221) and there was a significant increase of PC among workers hired before 1950 (O=18, SMR=172, 95% CI=102-273) (Straif *et al.*, 1998).

Conclusion: risk of PC due to occupational title in German rubber plants

This study did not provide convincing evidence that specific jobs within the rubber industry posed an increased risk of PC, although some data showed that PC incidence did increase with duration of employment.

Polish plants

Wilczynska and co-workers assessed the health effects of employment in a tyre manufacturing plant in Poland (Wilczynska *et al.*, 2001). The cohort consisted of 17747 (11660 men and 6078 women) workers employed in the rubber plant for at least three months during 1950-1995. Personal data and employment history for 94% of employees were obtained from personnel records from the company. For those of the cohort that had died, death certificates were obtained for 94.2% and the cause of death coded according to the Ninth Revision of the International Classification of Disease. The general population of Poland was used as the reference group. The cohort was subdivided into male and female, those working for <5 years or >5 years, and also according to the type of job the worker carried out. Those that carried out several jobs were classified as that with the longest employment in one area. A decreased risk, although not statistically significant, of PC was observed (O=8, SMR=87, 95% CI=38-181). Similarly, a deficit of PC was seen in employees working <5 years (O=3, SMR=97, 95% CI=20-283) and >5 years (O=5, SMR=82, 95% CI=27-191). However, in the sub-cohort of workers employed in the production of tyres and inner tubes, a slight excess of PC was observed (O=4, SMR=113, 95% CI=31-289) as well as working in storage areas (O=1, SMR=250) and other areas of work within the factory (O=1, SMR=296), although none of the observations were

statistically significant. Due to having only one case of PC, 95% CI were not calculated for some work areas (Wilczynska *et al.*, 2001).

Conclusion: risk of PC due to occupational title in Polish rubber plants

No convincing evidence was reported to suggest an excess risk for workers in different areas of the rubber industry. However, 56% of the participants were approximately 50 years of age and relatively few cases of PC were observed.

Unknown location

Mancuso and co-workers attempted to define more adequately the population at risk in a given rubber plant by dividing the cohort into office or non-office workers and subsequently, into departments and chemical exposure (Mancuso *et al.*, 1968). The cohort, comprising 188 office white males, 78 office white females, 1380 non-office white males, and 212 non-office white females, employed between 1938 and 1939, was followed until 1964. Personnel information including employment history was obtained from company records and from Social Security Administration. All death certificates were obtained and were coded according to the Sixth Revision of the International Statistical Classification of Diseases, Injuries or Causes of Death. The cohort was divided into five departments: office, compounding, milling and calendering, curing and tyre building, other miscellaneous departments, and unidentified departments. Two deaths due to PC were observed in the cohort, both deaths occurring in the non-office group, with no deaths being observed in the office group. One employee died after a seven year employment in the compounding, milling and calendering department and was aged 45-64, whereas the other worker was employed for ten years in the miscellaneous department and was aged 45-64 (Mancuso *et al.*, 1968). In view of the very small numbers involved (an isolated case in two work areas) no conclusions can be drawn from these data.

Andjelkovich studied a cohort of 8418 white male production workers who were retired or active as of 1964 and aged between 40 and 84 years of age (Andjelkovic *et al.*, 1977). Ninety seven percent of the cohort was followed for ten years until 1973 and over 98% of the cohort had worked for at least ten years at the rubber plant. Of the 8418 males in the cohort, 2373 died during the ten year follow up period, and the cause of death was obtained

from death certificates and was coded according to the Eighth Revision of the International Classification of Diseases. Data regarding the date of employment and termination of employment, and work history were obtained from personnel records. As a control for each occupational title, the rest of the cohort of rubber workers was used. The incidence of PC was examined for all occupational titles within the rubber plant. The only group of workers for which data were reported for PC were those employed in general service, in whom an excess of PC was observed (O=10, SMR=212) in more than one age group (Andjelkovic *et al*., 1977). The SMR relative to the general population was not calculated.

Conclusion: risk of PC due to occupational title in rubber plants of unknown location

In view of the limitations of these studies no definite conclusions can be drawn.

Overall conclusion: risk of PC due to occupational title

Several jobs within the rubber industry appear to be associated with a small increase in mortality due to PC but in view of the limitations of the studies no definite conclusions can be drawn. Furthermore most authors concluded that the excess risk was not due to a common exposure as there was no apparent link between the jobs in which the excess PC was observed.

Chemicals increasing risk of PC

Three studies have been retrieved that investigated the incidence of PC following different exposures within the rubber industry. Two studies were from US and one was from Germany.

US plants

In order to examine the associations between specific cancers with different solvents used in the rubber industry, a case-control study carried out by Wilcosky and co-workers, followed a cohort of 6678 active and retired male rubber plant workers for a 10-year period, beginning in 1964 (Wilcosky *et al.*, 1984). These workers from a rubber plant in Akron, were aged between 40-84 at the beginning of the study. A trained nosologist coded any deaths that occurred according to the Eighth Revision of the International Classification of Diseases. A 20% age-stratified sample of the cohort served as a control. To reconstruct the workers past exposures, product specifications and operating procedures

indicated which solvents were authorised for use during each stage of the tyre manufacture. Such documents gave the history of solvent usage per year and operational area. Worker exposures were then linked to the solvent data via work history records, which give information regarding the job title, department, and duration of employment in each job. Exposure was defined as the presence of the worker in a process area in which a solvent was authorised for use. Only workers with cumulative exposures for >1 year were included in analysis. The authors acknowledged that this method of classifying exposures might lead to misclassification of workers as exposed, as although areas were authorised to use solvents, they may not have actually been used. The data obtained indicated that PC was not significantly associated with any of the solvents used, and most odds ratios (ORs) were <2 (carbon tetrachloride, OR=1.3, n=12; xylenes, OR=1.5, n=8; carbon disulfide, OR=1.5, n=11; ethyl acetate, OR=1.93, n=5; acetone, OR=1.7, n=4; VM&P naphtha, OR=1.6, n=4) with the exception of toluene (OR=2.6, n=3). In view of the small numbers involved 95% CI were not calculated (Wilcosky *et al.*, 1984) and no definite conclusions can be drawn.

Collins and co-works investigated the mortalities of workers at a rubber plant in Nitro, US, with respect to exposure to 2-mercaptobenzothiazole (MBT) (Collins *et al.*, 1999). 2-Mercaptobenzothiazole is a rubber chemical accelerator that improves the vulcanisation process that stabilises rubber by creating strength and elasticity. The original cohort study, carried out by Straus included 1059 white male production workers, assembled from work histories and social security records that worked full time between 1955 and 1977. The latest follow-up study was carried out between 1955 and 1996, adding 9 years onto the study. Vital status was obtained from company payroll and pension files. At the end of the follow-up period, 659 were still living, 393 had died and 7 were lost. 388 (99%) of all death certificates were obtained and coded by trained nosologists, according to the Eighth Revision of the International Classification of Diseases. Exposure to MBT in the form of dusts was assessed. The MBT workers estimated average exposure between 1934-1977 was measured. The highest estimated exposures occurred between 1943 and 1954, when average exposures exceeded 2 $\mu g/m^3$. Average exposure was lowest during early years and after 1970. Greatest exposure usually resulted from equipment repairs and accidental leaks, rather than normal operating procedures. Cumulative exposure to MBT was used to evaluate the exposure-response for PC. Cumulative years of exposure are the sum of daily

exposures divided by 365 days. The four categories of cumulative exposures were none, 0.01-1.9 mg/m3-years, 2-7.7 mg/m3-years and 8-129 mg/m3-years. Person-years for workers not exposed to MBT were included in the 'none' category. Rates were also evaluated according to the time since first exposure (<20 years, and >20 years). The original study had 23943 person-years of observation, and 6404 in the update. Data obtained from the original study showed that the observed numbers of deaths from PC was greater than expected (O=7, E=3.9, SMR=1.8 (as cited by authors), 95% CI=0.7-3.7). However, data from the follow-up study showed a deficit in cases of PC (O=1, E=3.7, SMR=0.3, 95% CI=0-1.5). When combining the data, the incidence of PC was as expected (O=8, E=7.6, SMR=1.1, 95% CI=0.5-2.1) (Collins *et al.*, 1999). There was no evidence for any increased risk of PC in the study group.

Conclusion: risk of PC due to chemical exposure in US rubber plants

Neither of the studies provided any evidence that solvents or MBT were associated with an increase in PC.

German plants

A cohort of 8933 German rubber workers, who were hired after 1950 and were either still active (6875) or retired (2058) in 1981, were followed-up for mortality until 1991 (Straif *et al*., 2000). All workers had been employed for at least one year in the rubber factory. Health insurance data, personnel files and German population registries were used to determine vital status of the cohort members (94.8%). Work histories were reconstructed with cost centre codes that allowed identification by employment in specific areas. Death certificates were obtained from the health departments and the cause of death coded by a nosologist according to the Ninth Revision of the International Classification of Disease. Retrospective semi-quantitative estimates of exposures to nitrosamines (low, medium and high) were performed. N-Nitrosodiphenylamine (NDPhA), which was used as a retarder, is a potent transnitrosating agent. Hence workers employed in areas in which it was used such as curing, vulcanisation, and tube and tyre warehouse were categorised as having a high exposure to the nitrosamines, N-nitrosodimethylamine (NDMA) and N-nitrosomorpholine (NMOR). Medium concentrations of nitrosamines was detected in vulcanisation and subsequent production stages in which NDPhA were not used. Workers

employed in the production processes prior to vulcanisation, such as handling raw materials, weighing and mixing, extruding and calendaring, and component building were considered to have only low exposure to nitrosamines. The authors described the nitrosamine concentrations in the low exposure category to be between 0-2.5 $\mu g/m^3$, the medium exposure category to be 2.5-15 $\mu g/m^3$ and the high exposure category to be >15 $\mu g/m^3$.

Exposures within the factory were categorised according to job and members of the cohort were classified into exposure categories 1 and 2 (table 1) and hazard rate ratios for medium (RRm) and high (RRh) exposures were calculated ($[O_{treatment}/E_{treatment}] / [O_{low\ exposure}/ E_{low\ exposure}]$). The authors used workers in the low exposure group as the reference.

Table 1. Definition of exposure categories

	High exposure	Medium exposure
Exposure category 1	Workers employed at least 1 year in cost centre codes with high exposures	Workers employed less than 1 year at medium or high exposures
Exposure category 2	Workers employed at least 10 year in cost centre codes with high exposures	Workers employed less than 0.5 years at medium or high exposures

Twenty six mortalities due to PC were observed in the cohort. Data show a non-significant exposure-response relationship, which was similar for both exposure categories (exposure category 1, RRm=1.4, 95% CI=0.5-3.8, RRh=2.2, 95% CI=0.9-5.6, χ^2=2.42; exposure category 2, RRm=1.6, 95% CI=0.7-3.7, RRh=2.1, 95% CI=0.7-6.2, χ^2=2.42) (Straif *et al.*, 2000).

Conclusion: risk of PC due to chemical exposure in German rubber plants

This study did not provide convincing evidence that nitrosamines were associated with an increase in PC.

Overall conclusion: risk of PC due to chemical exposure

Overall, none of the studies provide convincing evidence that the incidence of PC was related to chemical exposure in the rubber industry

Literature and systematic reviews

Kogevinas carried out a literature review of all case-control and cohort studies from the rubber industry to summarise the evidence on potential risks of cancer to workers (Kogevinas *et al.*, 1998). This study showed that an excess risk of PC was found in three of the cohort studies investigated (Bernardinelli *et al*., 1987; Norseth *et al.*, 1983; Solionova and Smulevich, 1993; Weiland *et al.*, 1996), and in the industrial products department of the Akron cohort (Delzell 1984). No excess risks were seen in four studies (Gustavsson *et al*., 1986; Norseth *et al.*, 1983; Sorahan *et al.*, 1989; Szeszenia-Dabrowska *et al.*, 1991) or in the aerospace or reclaim departments of Akron rubber plant (Delzell and Monson, 1984; Delzell and Monson, 1985). From the case-control studies, no excess were observed.

Similarly, Stewart and co-workers carried out a meta-analysis of risk estimates for PC related to the tyre and rubber industry (Stewart *et al*., 1999). The authors investigated 20 studies, including 15 cohort and 5 case-control studies. Eight studies were discarded due to having duplicate populations, hence the results of nine cohort and three case-control studies were finally pooled to gain an overall estimate of risk of PC for workers in this industry. The SMRs for the cohort studies ranged from 58-518 and the ORs for the case-control studies ranged from 0.1-1.9. Within these case-control studies, Goldsmith looked at PC mortality (Goldsmith *et al*., 1980) whereas Elghany noted PC incidence (Elghany *et al.*, 1990). When pooling data from the different studies, the SMR for the nine cohort studies was 101 (95% CI= 93-110). The study carried out by Sorahan contributed to the heterogeneity of the studies and when excluded, the remaining eight studies were homogeneous (SMR=105, 95% CI=96-115). The pooled OR for the three case-control studies was 1.10 (95% CI=0.94-1.29). The two incidence case-control studies were also considered separately, giving a pooled OR of 0.99 (95% CI=0.3-3.25). When all studies were combined, the OR was 1.03 (95% CI=0.96-1.11). Again, upon exclusion of the Sorahan study, the remaining studies were homogeneous, giving a OR of 1.06 (95% CI=0.98-1.15).

Overall, the authors concluded that the results of the meta-analysis suggest that there is no significant excess risk for PC among workers employed in tyre and rubber manufacture. However, a few studies reported excess risks for PC in specific jobs within the manufacturing industry, including material conservation (Monson and Fine, 1978), batch preparation (Goldsmith *et al*., 1980), and compounding, mixing, calendaring (McMichael *et al.*, 1976b). From the meta-analysis, the authors do not make any conclusions regarding the risk of PC from different job categories (Stewart *et al.*, 1999).

Discussion

This report was carried out to further investigate the risk of PC in workers employed in the rubber industry. The report looked at studies that analysed data from factories as a whole, and also those that tried to assess possible risks associated with specific job categories. In addition, an attempt was made to correlate these findings with possible chemical exposures. Within each category, studies were subdivided according to geographical location of the rubber plant.

Studies carried out in rubber plants in different geographical regions revealed some differences. In US and Germany, the overall data did not provide convincing evidence of an increased risk of PC in rubber plant workers. In contrast, British studies pointed to a significant deficit of PC. This may be ascribed to the healthy worker effect. Data obtained from the Italian rubber industry reported a significantly higher SMR. However, this study was based on only 2 deaths from PC out of a cohort of 4917 participants, in which 143 deaths occurred due to other causes. The authors also stated that the follow-up period used was relatively short, resulting in the observed deaths being lower than would be expected with longer follow-up times, giving an underestimation of the SMR (Bernardinelli *et al.*, 1987). Overall the evidence does not suggest that rubber workers are at increased risk of PC. This was supported by the results of a meta-analysis on PC and workers in the tyre and rubber industries (Stewart *et al*., 1999).

A number of studies have investigated PC and specific job categories in the rubber industry. In studies in which the analyses were undertaken on a cohort made up of the total male population of workers within the plant, regardless of their job title, a 'dilution factor' may arise with regard to the effects of any specific chemical. In order to change the mortality pattern of the total population of the cohort, the toxicological effects would have to be strong (Bernardinelli *et al.*, 1987). Therefore, excess deaths due to a certain exposure in a specific department may be masked leading to an underestimation of the number of cases (Mancuso *et al*., 1968).

Several different, seemingly unrelated, jobs categories were retrieved in which a small excess of PC mortality was documented, including compounding and mixing (Andjelkovic

et al., 1977; Goldsmith *et al.*, 1980; McMichael *et al.*, 1976a), cement mixing (McMichael *et al.*, 1976a), janitoring and trucking (Andjelkovic *et al.*, 1977; McMichael *et al.*, 1976b; Straif *et al.*, 1998), calendering and plystock handling (McMichael *et al.*, 1976b), salary (Goldsmith *et al.*, 1980), miscellaneous tyre area (Monson and Nakano, 1976b), material conservation and final finish (Monson and Fine, 1978), maintenance (Straif *et al.*, 1998; (Monson and Fine, 1978) and working in storage areas (Wilczynska *et al*., 2001). Table 2 shows the excess risk of PC in workers employed in different departments within rubber industries in different geographical locations.

Some of these job categories share common chemical exposures. Employees have a potential exposure to organic solvents in areas including cement mixing, calendering, plystock handling, product building, finishing, repair and maintenance, and have been shown to have an excess of PC in different studies (figure 1). However, workers in other areas, also with potential exposure to such solvents do not have an increased risk of PC i.e. workers in repair, extrusion and product fabrication. Similarly, workers in areas suggested to have an excess risk of PC are potentially exposed to nitrosamines at low concentrations, including compounding and mixing (0.1-0.9 $\mu g/m^3$ NDMA and 0.1-2.0 $\mu g/m^3$ NMOR), calendaring (0.1-2.0 $\mu g/m^3$ NDMA and 0.1-9.0 $\mu g/m^3$ NMOR), and product building (0.1-1.0 $\mu g/m^3$ NDMA and 0.5-3.0 $\mu g/m^3$ NMOR), whereas those working in extrusion and curing areas, departments in which excess risk of PC was not demonstrated, are potentially exposed to medium or high concentrations of nitrosamines (maximum concentration of 130 $\mu g/m^3$ NDMA and 140 $\mu g/m^3$ NMOR measured). Maintenance workers are usually exposed to high concentrations of chemicals for short periods during repairs, the most likely causal exposure being to cutting oils (Monson and Fine, 1978). Furthermore, in both of these jobs, workers may be potentially exposed to nitrosamines through metal working fluids. Straif and co-workers reported that exposure to such fluids has been related to PC in automobile workers. However, association was observed between straight oil metal working fluids and not for synthetic oil metal working fluids, which are usually most heavily contaminated with nitrosamines (Straif *et al.*, 2000). Overall, the lack of a dose-response relationship suggests that there is not an association between nitrosamine exposure and PC.

Table 2. Excess PC cases observed in different departments within the rubber industry

Department	Location	Author	Results
Compounding and mixing	US	McMichael *et al.*, 1976a	Overall SMR for PC=119.
	US	McMichael *et al.*, 1976b	RR_{as}=1.6, 99.9% CI=1.2-2.3.
	US	Goldsmith *et al.*, 1980	>1 month, n=17, OR=2.8; >24 months, n=14, OR=2.8; >60 months, n=11, OR=3.0.
Calendering and plystock	US	McMichael *et al.*, 1976b	RR_{as}=2.4, 99.9% CI=1.9-3.3.
Cement mixing	US	McMichael *et al.*, 1976a	Overall SMR for PC=119.
	US	McMichael *et al.*, 1976b	RR_{as}=1.6, 99.9% CI=1.2-2.3.
Tyre building	US	Monson & Nakano, 1976b	O=12, E=8.8, SMR=140.
	Poland	Wilczynska *et al.*, 2001	O=4, SMR=113, 95% CI=31-289.
Salary	US	McMichael *et al.*, 1976b	RR_{as}=3.5, 99.9% CI=2.8-4.6.
	US	Goldsmith *et al.*, 1980	>1 month, n=13, OR=2.8, χ^2=5.41; > 24 months, n=7, OR=2.0, χ^2=1.44.
Maintenance	US	Monson & Fine, 1978	n=4.2, O=1, E=2, RR=2.1.
	Germany	Straif *et al.*, 1998	O=27, SMR=152, 95% CI=99-221.
General service (janitoring and trucking)	US	McMichael *et al.*, 1976a	Overall SMR for PC=119.
	Germany	Straif *et al.*, 1998	O=27, SMR=152, 95% CI=99-221.
	Unknown	Andjelkovic *et al.*, 1977	O=10, SMR=212.
Final finish	US	Monson & Fine, 1978	n=88, O=4, E=1.2, RR=2.4.
Storage	Poland	Wilczynska *et al.*, 2001	O=1, SMR=250.
Material conservation	US	Monson & Fine, 1978	n=28, O=4, E=0.28, RR=7.6.

Within the compounding and mixing area, which also included batch preparation, workers are exposed to solid materials such as accelerators, antioxidants, and carbon black in particulate form and have a potentially high exposure of carbamates and heavy metal oxides (Andjelkovic *et al.*, 1977; McMichael *et al.*, 1976b). In addition, the association with compounding and mixing is of interest due to the use of cadmium oxides as

vulcanisation accelerators (McMichael *et al.*, 1976a), as cadmium has been suggested to be a risk factor for PC. Although a number of studies reported statistically significant increases in PC mortality in a number of different areas within the rubber plant, such excesses appeared in disparate areas that had few common exposure factors. In addition, the numbers of cases of PC observed in each division of the plant were very small.

McMichael observed that the ratios of exposure rates in their study were influenced by the composition of the workforce, as a greater number of black employees worked in the compounding and mixing area, and suggested a likelihood of race confounding in the association between PC and compounding and mixing (McMichael *et al.*, 1976b). The excess risk of PC in workers employed in compounding and mixing was only observed in plants situated in the US.

On of the major problems with a study of this type is that the workers employment within the industry is likely to change periodically, resulting in exposure to different chemicals. Furthermore, employees potentially exposed to chemicals in the specific areas are not confined to production workers, but also encompasses scientific personnel, chemists, engineers, managers and supervisory foremen, who are actually classified as office workers. Employees in areas close in proximity may also be at risk of chemical exposure. Most studies classified workers based on the last position held, or longest position held, without taking into account the whole job history. This approach may lead to misclassification in cases where employees may have been promoted to office work after working in production, hence were classified as office staff despite previous chemical exposures, or when workers changed jobs to ones that had less of a risk of chemical exposure (Mancuso *et al.*, 1968). The latter may explain the association of PC with janitoring, as this may be an artefact of job mobility, due to workers being assigned jobs such as elevator operating, which is classified as janitoring, following or during illness (Straif *et al.*, 2000).

Few studies used in this report measured chemical exposure within the rubber plant. Exposures reported are usually based on duration of employment or based on job title and chemical registrations. This approach is often misleading and could result in an

overestimation of exposed workers, as although certain departments may have been registered to use certain chemicals, in practice, such chemicals may not have been used.

Final conclusion

Overall, there is no convincing evidence of an increased risk of PC in rubber workers as a whole.

Abbreviations

CI	Confidence interval
E	Expected
IARC	International agency for the Research on Cancer
MBT	2-mercaptobenzothiazole
O	Observed
OR	Odds ratio
OTG	Occupational titled group
OT	Occupational title
PC	Prostate cancer
RR	Relative risk
RRas	Age standardised risk ratio
RRh	Rate ratio for high exposures
RRm	Rate ratio for medium exposures
SMR	Standardised mortality ratio

References

Andjelkovic, D. A., Taulbee, J., and Symons, M. (1976). Mortality experience of a cohort of rubber workers, 1964-1973. *J Occup Med* **18**, 387-394.

Andjelkovic, D. A., Taulbee, J., Symons, M., and Williams, T. (1977). Mortality of rubber workers with reference to work experience. *J Occup Med* **19**, 397-405.

Bernardinelli, L., de Marco, R., and Tinelli, C. (1987). Cancer mortality in an Italian rubber factory. *Br J Ind Med* **44**, 187-91.

Collins, J. J., M.E., S., and S.G., R. (1999). Mortalities of workers at the Nitro plant with exposure to 2-mercaptobenzothialzole. *Occup. Environ. Med.* **56**, 667-671.

Delzell, E., and Monson, R. R. (1981). Mortality among rubber workers. III. Cause-specific mortality, 1940-1978. *J Occup Med* **23**, 677-84.

Delzell, E., and Monson, R. R. (1984). Mortality among rubber workers: VII. Aerospace workers. *Am J Ind Med* **6**, 265-71.

Delzell, E., and Monson, R. R. (1985). Mortality among rubber workers: IX. Curing workers. *Am J Ind Med* **8**, 537-44.

Elghany, N. A., Schumacher, M. C., Slattery, M. L., West, D. W., and Lee, J. S. (1990). Occupation, cadmium exposure, and prostate cancer. *Epidemiology* **1**, 107-15.

Goldsmith, D. F., Smith, A. H., and McMichael, A. J. (1980). A case-control study of prostate cancer within a cohort of rubber and tire workers. *J Occup Med* **22**, 533-41.

Gustavsson, P., Hogstedt, C., and Holmberg, B. (1986). Mortality and incidence of cancer among Swedish rubber workers, 1952-1981. *Scand J Work Environ Health* **12**, 538-44.

IARC (1982). The rubber industry: *International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans*, Lyon.

IARC (1987). The rubber industry (Group 1). *International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans.*, Lyon.

Kogevinas, M., Sala, M., Boffetta, P., Kazerouni, N., Kromhout, H., and Hoar-Zahm, S. (1998). Cancer risk in the rubber industry: a review of the recent epidemiological evidence. *Occup Environ Med* **55**, 1-12.

Mancuso, T. F., Ciocco, A., and el-Attar, A. A. (1968). An epidemiological approach to the rubber industry. A study based on departmental experience. *J Occup Med* **10**, 213-32.

McMichael, A. J., Andjelkovic, D. A., and Tyroler, H. A. (1976a). Cancer mortality among rubber workers: an epidemiologic study. *Ann N Y Acad Sci* **271**, 125-37.

McMichael, A. J., Spirtas, R., Gamble, J. F., and P.M., T. (1976b). Mortality among rubber workers: relationship to specific jobs. *J Occup Med* **18**, 178-185.

McMichael, A. J., Spirtas, R., and Kupper, L. L. (1974). An epidemiologic study of mortality within a cohort of rubber workers, 1964-72. *J Occup Med* **16**, 458-64.

Monson, R. R., and Fine, L. J. (1978). Cancer mortality and morbidity among rubber workers. *J Natl Cancer Inst* **61**, 1047-53.

Monson, R. R., and Nakano, K. K. (1976a). Mortality among rubber workers. I. White male union employees in Akron, Ohio. *Am J Epidemiol* **103**, 284-96.

Monson, R. R., and Nakano, K. K. (1976b). Mortality among rubber workers. II. Other employees. *Am J Epidemiol* **103**, 297-303.

Norseth, T., Andersen, A., and Giltvedt, J. (1983). Cancer incidence in the rubber industry in Norway. *Scand J Work Environ Health* **9 Suppl 2**, 69-71.

Solionova, L. G., and Smulevich, V. B. (1993). Mortality and cancer incidence in a cohort of rubber workers in Moscow. *Scand J Work Environ Health* **19**, 96-101.

Sorahan, T., Parkes, H. G., Veys, C. A., and Waterhouse, J. A. (1986). Cancer mortality in the British rubber industry: 1946-80. *Br J Ind Med* **43**, 363-73.

Sorahan, T., Parkes, H. G., Veys, C. A., Waterhouse, J. A., Straughan, J. K., and Nutt, A. (1989). Mortality in the British rubber industry 1946-85. *Br J Ind Med* **46**, 1-10.

Stewart, R. E., Dennis, L. K., SDawson, D. V., and Resnick, M. (1999). A Meta-analysis of risk estimates for prostate cancer related to tire and rubber manufacturing operations. *J. Occup. Environ. Med.* **41**, 1079-1084.

Straif, K., Weiland, S. K., Bungers, M., Holthenrich, D., Taege, D., Yi, S., and Keil, U. (2000). Exposure to high concentrations of nitrosamines and cancer mortality among a cohort of rubber workers. *Occup Environ Med* **57**, 180-187.

Straif, K., Weiland, S. K., Werner, B., Chamless, L., Mundt, K. A., and Keil, U. (1998). Workplace risk factors for cancer in the German rubber industry: part 2. Mortality from non-respiratory cancers. *Occup Environ Med* **55**, 325-332.

Straughan, J. K., and Sorahan, T. (2000). Cohort mortality and cancer incidence survey of recent entrants (1982-91) to the United Kingdom rubber industry: preliminary findings. *Occup Environ Med* **57**, 574-6.

Szeszenia-Dabrowska, N., Wilczynska, U., Kaczmarek, T., and Szymczak, W. (1991). Cancer mortality among male workers in the rubber Polish industry. *Polish J. Occup. Med. Environ. Health* **4**, 149-157.

Weiland, S. K., Mundt, K. A., Keil, U., Kraemer, B., Birk, T., Person, M., Bucher, A. M., Straif, K., Schumann, J., and Chambless, L. (1996). Cancer mortality among workers in the German rubber industry: 1981-91. *Occup Environ Med* **53**, 289-98.

Wilcosky, T. C., Checkoway, H., Marshall, E. G., and Tyroler, H. A. (1984). Cancer mortality and solvent exposures in the rubber industry. *Am Ind Hyg Assoc J* **45**, 809-11.

Wilczynska, U., Szadkowska-Stanczyk, I., Szeszenia-Dabrowska, N., Sobala, W., and Strzelecka, A. (2001). Cancer mortality in rubber tire workers in Poland. *Int J Occup Med Environ Health* **14**, 115-25.