CANCER MORTALITY AMONG RUBBER WORKERS: AN EPIDEMIOLOGIC STUDY *

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INTRODUCTION

Chemical carcinogenesis is today an accepted phenomenon, based partly on a variety of occupational epidemiologic studies. In 1895, an increased risk of bladder cancer was reported for workers in the dyestuffs and chemical industries.[1] In 1974, excess deaths from angiosarcoma of the liver were reported in the polyvinyl chloride manufacturing industry.[2] In the intervening eighty years, similar epidemiologic studies have been carried out in many other "chemical" industries, including the rubber industry.

The rubber-tire manufacturing industry uses a vast and ever-changing variety of organic and inorganic chemicals. Further, because of the high temperatures involved in several of the processes. there are many chemical reaction by-products produced, most of which remain unidentified. Among the chemical ingredients now or previously used are various proven or suspected carcinogens, such as β-naphthylamine. benzene. asbestos (in talc dust), and various nitrosamines.

Previous epidemiologic studies of the rubber industry, in Great Britain and in the United States, have identified excess deaths from several types of cancer. Associations of some of these cancers with specific jobs have also been reported. For the period 1929–31. the British Registar General reported that rubber workers showed a 10% total mortality excess. compared with national mortality data, and that this excess derived from cancer deaths.[3] The United States Department of Health, Education. and Welfare has reported that, for male rubber workers dying in 1950. when compared with death rates in male workers in all manufacturing industries. there was an 8% excess of cancer deaths. The greatest excesses were for cancers of the large bowel (30%), respiratory system (18%). and the lymphatic ana hematopoietic system (54%).[4]

Mancuso, in 1949. reported an elevated proportion of deaths due to cancer for workers in the rubber and plastics industry in Ohio (the center of the U.S. rubber industry).[5] In particular. he reported a proportional mortality excess from respiratory, genitourinary. and central nervous system cancers. Subsequently, Mancuso et al. analyzed mortality in a cohort of 1877 rubber workers between 1940 and 1968, finding. firstly. excess cancer death rates in workers in the compounding, milling. calendering, and curing areas (see FIGURE 7 below), and secondly, an excess mortality (for the total cohort) from cancers of the gall bladder, bile ducts and salivary glands.[6, 7] More recently, a number of

* This research was conducted within the Occupational Health Studies Group in the School of Public Health, and drew upon the efforts of many individuals.

other associations between specific cancers and jobs within the rubber industry have been reported by Mancuso, based on data from four separate rubber companies.[8]

In two recent, separate studies, McMichael et al. reported. firstly, excess death rates from cancers of the stomach, colon, prostate, and lymphatic and hematopoietic system in a cohort of 6678 rubber workers. and. secondly, an association between lymphatic leukemia in rubber workers and a work-history of solvent exposure.'' [10] Simultaneously, Monson and Nakano. in a preliminary analysis of a large cohort of rubber workers, reported excess death rates from leukemia, and cancers, of the bladder, stomach, pancreas and large bowel.[11] Certain of these and Other cancers were associated with exposure to specific work areas.

In Great Britain, in 1954. Case and Hosker confirmed a suspected excess of bladder cancer in rubber workers.[12] Despite elimination of the presumed carcinogen (β-naphthylamine) from the production process, some persistence of a bladder cancer mortality excess was subsequently reported by Veys[13] and Adelstein.[14] In 1974, however. more than twenty years after the change, the report of a large mortality study in the rubber and cable-making industries stated: "No evidence is found of a continued excess risk of neoplasms of the bladder in people who entered the industry after 1949."[15] In that same study, Fox et al. found an excess total cancer mortality among rubber workers in the tire-manufacturing section, including particularly an excess for cancer of the bronchus and lung which. in turn, was highest for workers exposed to either the tire curing (vulcanization) process. or to jobs in the stores. packaging, and despatch area.

Despite the differences in location, time period. and methodology, these various epidemiologic studies of the rubber industry, demonstrate a general problem of excess cancer mortality. This present study has sought to determine the recent cancer mortality experience of U.S. rubber workers and, ultimately, to discover the specific jobs (and, where possible, the specific chemical or physical agents) associated with increased risk of cancer mortality.

METHODS

The Occupational Health Studies Group. within the Schooi of Public Health, University of North Carolina. is under contract jointly- to the United Rubber Workers Union and four of the six major U.S. rubber companies to carry out a comprehensive occupational health research program. The need for such research was agreed upon by labor and management in their 1970 contract negotiations. Foremost within the research program to date has been the analysis of mortality during the past decade.

Four cohorts of male rubber workers were identified. at the major tire-manufacturing plant in each of the four rubber companies (designated as A, B, C, and D). Three of the plants are located in Akron, Ohio, and one in Wisconsin. Working from payroll, pension, life insurance, and other company records, the four historical populations of hourly (i.e., production) male rubber workers — active or retired — and aged 40 to 84 at 1.1.64 were identified. (For company D, the cohort was identified at 1.1.63.)

The ten-year mortality experience of these four cohorts was determined from death claims filed with the companies under the group life insurance policy in

force since the nineteen fifties. The completeness of death ascertainment was confirmed by cross-checking internally against other company records. Within one of the cohorts, an external check was made against the files of the Internal Revenue Service, confirming that a random sample of apparent cohort survivors were in fact still alive.

Approximately 1% of cohort workers were lost to follow-up, being initially active workers who subsequently terminated their employment and went to work elsewhere. Of the remaining study subjects, death certificates were obtained for 98% of those who died. These were coded by a certified nosologist, according to the Eighth Revision of the International Classification of Diseases.

The mortality experience of these four cohorts was evaluated by the calculation of race-age-standardized mortality ratios **(SMR).** (Because of the decline in the validity of cause-of-death recording at very old ages, the few deaths above age 84 were excluded from the analysis.) The 1968 U.S. male population provided the ''standard'' race-age-specific death rates, for calculating the expected deaths. Choice of this particular standard population introduces an underestimation of mortality. because an active industrial workforce. not exposed to significant work-related health hazards, is normally healthier than a similarly aged sample of the general population.''. In a hazard-free occupational environment, an industrial population, when compared to the general population, could reasonably be expected to have an SMR of about 80. (Indeed, according to Social Security actuarial data, the survival experience of the general industrial working population may be 40% better than the general population.) [17] One procedure that can partially eliminate this underestimation of mortality is to compare each cause-specific SMR to the underlying all-causes SMR.

In examining the association of specific cancers to specific work exposures, detailed work histories of individual workers were obtained from the companies. The diversity of job types. combined with the individual's job mobility, presents a formidable task if the full range of work experience is to be taken into account (as opposed to using a single-classification approach, based on "most representative job," "most recent job." or "job at cohort-identification"). The techniques in this study to code and analyze an individual's total work experience have been described elsewhere.[18] The job classification scheme entails grouping jobs according to type of materials handled and/or production stage.

Results and Discussion

The age-composition of the study population is shown in TABLE 1. The two larger cohorts (companies A and C) were also of older average age. Overall. 41% of workers were aged 40–54 at cohort identification, 30% were aged 55–64 and 29% were aged 65–84. Retirement normally occurs at age 65 within the rubber industry. Of the total of 18,903 workers. 98% had worked for at least ten years in the rubber industry at the time of cohort identification, and the average employment duration was 25–29 years. For cohorts A, B, and C the Proportion of nonwhites ranged from 5–13%. Cohort D contained white males only.

FIGURE 1 shows the SMRs for deaths from all causes, for the four cohorts.

For each cohort, three SMRs are calculated: for ages 40–64, for ages 65–84, and for the full age-range 40–84. Three observations can be made:

1. Mortality is relatively greater at the older ages.
2. The individual cohort SMRs (for the age-range 40–84) vary between 82 and 98.†
3. The combined-cohorts SMR, for ages 40–84, is 94—suggesting some 10–15% excess of mortality in a population whose SMR could otherwise be expected to be in the range 80–85 if its members had not been exposed to work-place health hazards.

Of the total of 5106 deaths, 1014 were due to cancers. FIGURE 2 shows the individual and combined cohort SMRs for deaths due to cancer. Again, the cancer mortality is relatively greater at older ages, and there is approximately 10% variation among the four cohorts. For each of the 15 cancer SMRs shown, the corresponding all-causes SMR is lower, suggesting that in this population of rubber workers there is an excess of cancer deaths.

TABLE 1

AGE COMPOSITION, BY PERCENTAGE, OF THE FOUR MALE RUBBER-WORKER COHORTS, AT 1/1/64
(COLUMN PERCENTAGE)

	Company				All Four Companies
Age	A	B	C	D	
40–54	38%	59%	37%	58%	41%
55–64	30%	24%	31%	39%	30%
65–84	32%	17%	32%	13%	29%
Total Number	6,678	1,339	8,938	1,948	18,903

The cancer mortality experience of each of these four cohorts has been analyzed in detail. (Further, proportional mortality analyses have been carried out at a number of other smaller plants, for which the underlying populations at risk have not been identified.) The results of these total-population analyses are presented before considering the relationship of specific cancers to specific job categories within the rubber industry.

The SMRs for four major cancers of the digestive system are shown in FIGURE 3, and are calculated for the four cohorts combined. For each cancer, three SMRs are shown: for ages 40–64, 65–84, and for the full age-range 40–84. The four individual cohort SMRs, for ages 40–84, are also indicated.

For stomach cancer, there is a clear excess mortality, which is relatively greater at younger ages. Overall, the stomach cancer SMR of 148 represents

† Because of the indirect age-adjustment used in computing an SMR, strictly the individual cohort SMRs are not directly comparable to one another; however, the error involved in this comparison is only slight, of the order of 2–3%.

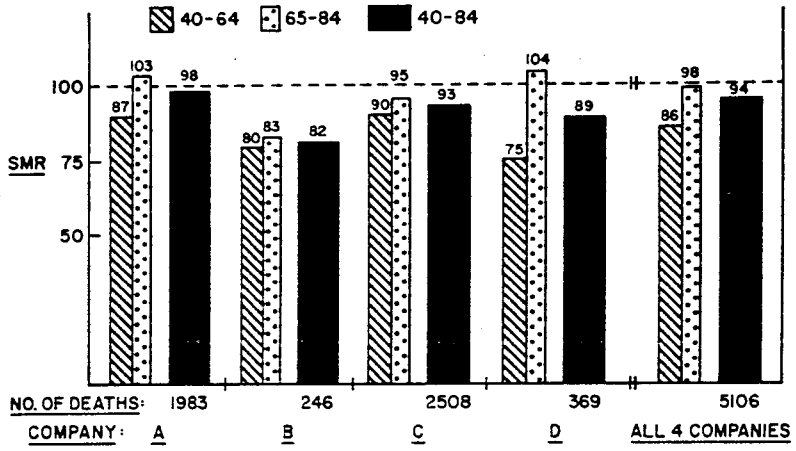

FIGURE 1. Race-age-standardized mortality ratios (SMR) for deaths from all causes, four cohorts of male rubber workers, 1964–73. Expected deaths were calculated from U.S. male race-age-specific death rates, 1968. (This applies also to FIGURES 2–5.

80 deaths where 54 were expected. Cancer of the colon shows a moderate excess, with an overall SMR of 116, while cancer of the rectum shows an SMR of 82. The two cohorts with highest SMRs for colon cancer (A and C), were lowest for rectal cancer, and vice versa. Cancer of the pancreas shows a slight excess, with an SMR of 103, when compared with the all-causes SMR of 94.

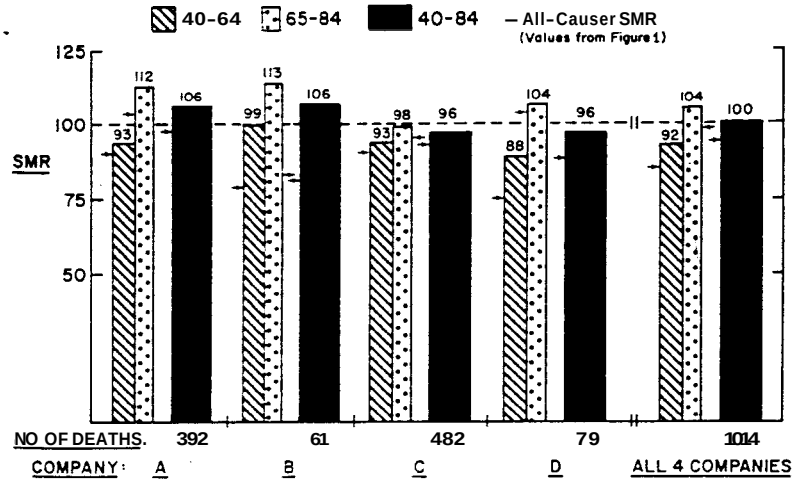

FIGURE 2. Race-age-standardized mortality ratios (SMR) for deaths from all cancers, male rubber workers, 1964–73. (See FIGURE 1 legend for calculation of expected deaths.)

(Cancers of the liver. gall bladder, and bile ducts, not shown here, totaled 12 deaths. representing a deficit of approximately 25% below expected.)

With respect to the excess stomach cancer death rates. the approximately *50%* excess shown here has also been found repeatedly in proportional mortality analyses at other plants. **A** detailed study of the specific work-exposure correlates of stomach cancer is currently under way, and is paying particular attention to the ingestion of carbon black (with adsorbed carcinogens such as benzpyrene), asbestos, and nitrosamines.

A case-control study of *72* colorectal cancer deaths and 716 matched controls, from company **A** (with an SMR of 123), found no statistically significant association with specific jobs, although the cases tended to have worked in rubber-batch preparation, milling, and maintenance jobs more than the controls.[19]

FIGURE 4 shows the combined-cohorts SMRs for respiratory, prostate, bladder, and central nervous system cancers. With the exception of cancer of the prostate. with an overall SMR of 119, no excess deaths from the other three cancer types were consistently observed. Respiratory cancer mortality was consistently at or slightly below the expected figure. which is particularly interesting in view of the recent report of an SMR for bronchogenic cancer of 134 in a population of 16,035 British rubber-tire workers (also calculated with use of the national population as standard).[15] Moderate proportional excesses of lung cancer, however, were observed at a number of other plants. underscoring the important consideration that working environments and their attendant health-hazards may differ significantly between plants.

Bladder cancer mortality. although mildly elevated in *two* of the cohorts (B and C). is also slightly below expected in the combined-cohorts SMR.

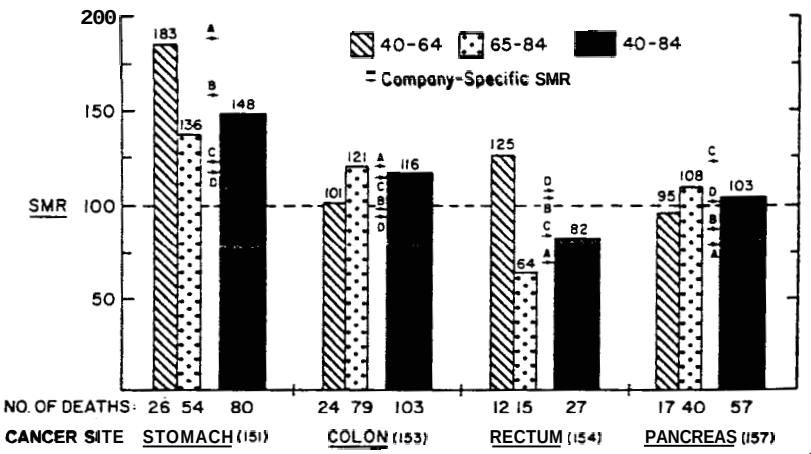

FIGURE 3. Standardized mortality ratios (SMR) for deaths due to selected cancers of the digestive system; white male rubber workers, all 4 companies, 1964–73. Figures in parentheses after cancer site indicate ICDA (International Classification of Diseases, Adapted) code, Eighth Revision. (See **FIGURE 1** legend for calculation of expected deaths.)

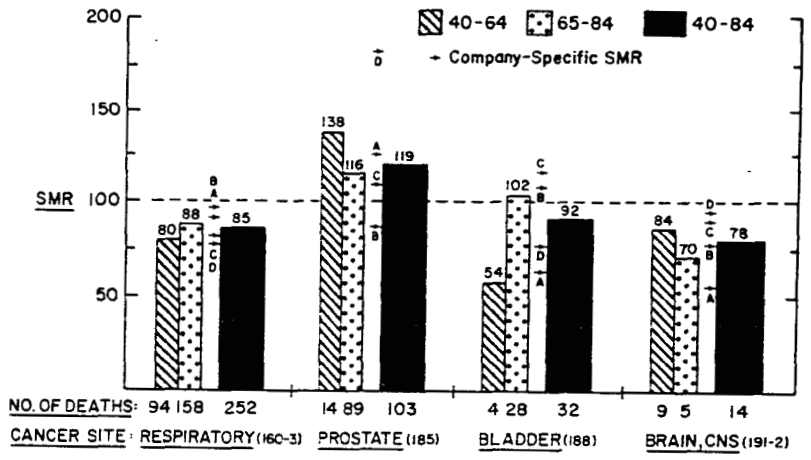

FIGURE 4. Standardized mortality ratios (SMR) for deaths due to selected cancers of the respiratory, urogenital, and central nervous systems; white male rubber workers, all 4 companies, 1964–73. (See FIGURE 1 legend for calculation of expected deaths.)

Earlier British reports (see above) indicated a marked excess of bladder cancer deaths within the rubber tire industry, associated with use of β-naphthylamine as an antioxidant chemical. Subsequently, use of this chemical *per se* has been discontinued, although it has been found present as a contaminant in other chemicals. Other suspected bladder carcinogens (particularly aromatic amines) have more recently been used in the rubber industry. A large, hospital-based case-control study of bladder cancer in rubber workers in Akron, Ohio (the nation's "rubber industry capital") is therefore being conducted in order to identify the work-exposure correlates of bladder cancer. The important assumption underlying this study is that, even though the total population SMR for bladder cancer may show no significant elevation, there may still be minority groups of workers whose substantially increased risk of bladder cancer is being obscured.

None of the four cohorts showed an excess of brain or other central nervous system cancers. Mancuso has reported excess death rates for these cancers in various subgroups of rubber workers.[8, 20] However, with only 14 cases observed in all four cohorts, the analytic possibilities are limited. Some proportional mortality excesses for these cancers have been observed at other smaller plants (see also Reference 9).

The SMRs for neoplasms of the lymphatic and hematopoietic system are shown in FIGURE 5. For all such neoplasms, there is an overall SMR of 131, with an excess observed in each of the individual cohorts. For lymphosarcoma and Hodgkin's disease, the overall SMR is 129, and for all leukemias the overall SMR is 130. The SMR for lymphatic leukemia is markedly elevated, with values of 158 overall, and 291 in the younger age range.

Benzene was once the most widely used organic solvent in the rubber industry. In view of benzene's suspected leukemogenic potential,[21, 22] a case-

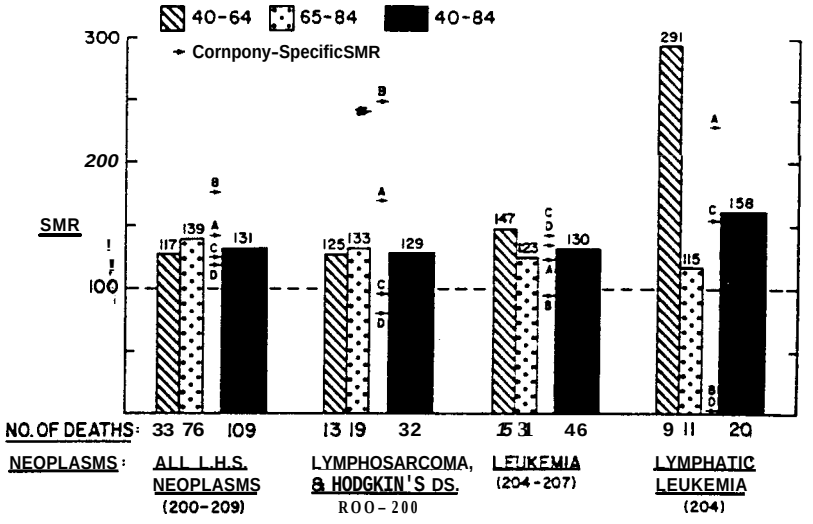

FIGURE 5. Standardized mortality ratios (SMR) for deaths due to neoplasms of the lymphatic and hematopoietic system: white male rubber workers, all 4 companies, 1964–73. (See **FIGURE** 1 legend for calculation of expected deaths.)

control study of leukemia deaths in all plants of company A was carried out.[10] For each death from, or with, leukemia, three individually matched controls (matched on plant, sex, race, and age, and known to have died of some other noncancer cause) were selected, and complete work histories were obtained for each study subject. Work histories were coded, blind. according to the general job-type classification system, and were also coded according to the presumed level of solvent exposure in each job, as assessed a priori by the research group's industrial hygienists.

The major production stages in the manufacture of rubber tires are shown in **FIGURE** 6. A number of jobs within the middle stages (boxes 3 through 8)

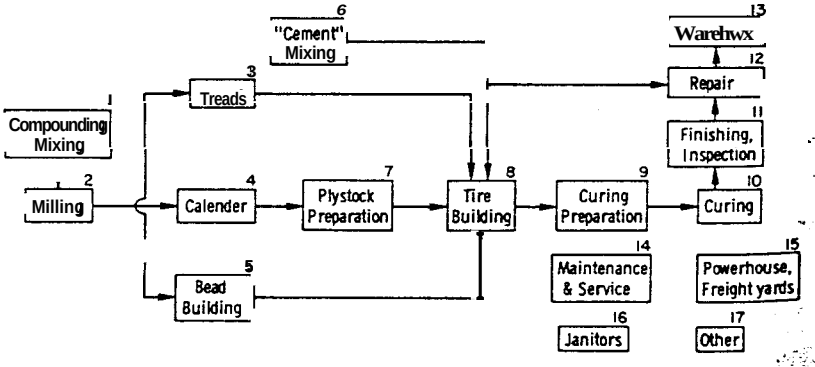

FIGURE 6. Diagrammatic representation of rubber tire production stages.

involve exposure to organic solvents, as do some latter jobs in finishing, repair, and maintenance. These jobs were grouped into high, medium, and low solvent-exposure categories. Jobs involving no apparent solvent exposure were grouped into seven functional constituents, such as Compounding and Mixing, Milling, Curing, and so on.

The association of myeloid leukemia with solvent exposure did not achieve statistical significance. However, in the case-control analysis of lymphatic leukemia, there was a strong association with solvent exposure, as summarized in FIGURE 7. The job categories are shown along the horizontal axis, and the vertical axis is the difference in exposure duration between cases and controls. For each of the three solventexposure categories, the cases on average were

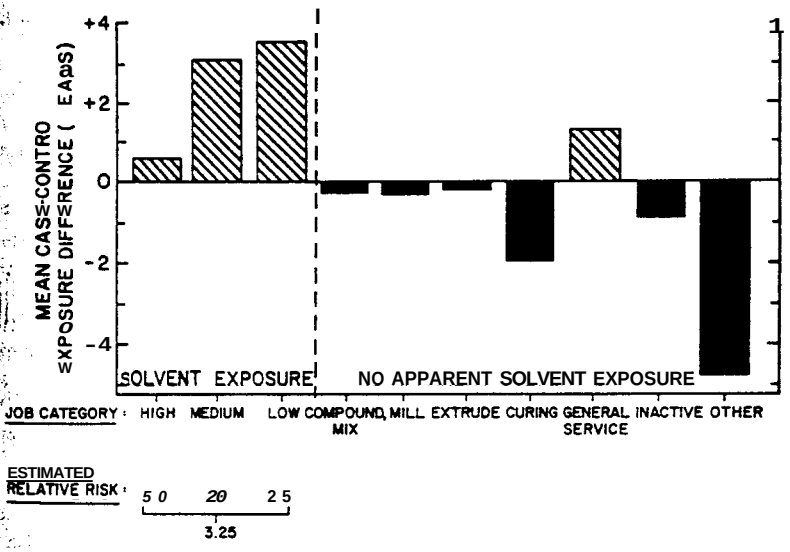

FIGURE 7. Mean difference in duration of exposure between 17 lymphatic leukemia cases and 51 individually matched controls, to job categories by level of solvent exposure. Note: the estimated relative risk of lymphatic leukemia for solvent exposed workers was calculated by "discordant matched sets" analysis.

exposed for several years more than their controls. Overall, cases experienced an average of eleven years of solvent exposure, compared *to* four years for controls For all other jobs (except General Service), the controls had had longer average exposure. The association between cases and exposure to General Service is quite plausible in terms of the solvent-exposure hypothesis. since many jobs in this category are itinerant. and—some involve cleaning and degreasing operations.

The estimates of relative risk shown beneath FIGURE 7 are based on discordant matched sets analysis, with exposure categorized as a "yes-no" variable. For workers in solvent-exposure jobs overall, there was a more than threefold increase in the risk of lymphatic leukemia. For those who worked in the high solvent-exposure area. the estimated increase in risk is fivefold.

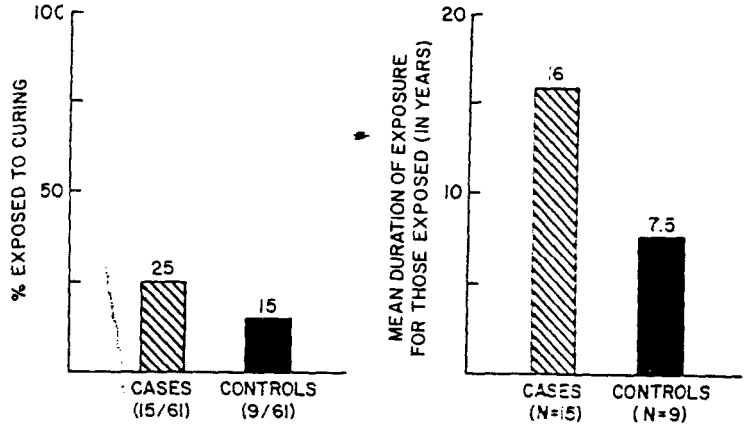

FIGURE 8. Comparison of 61 cases of lung cancer (ICDA. 8th Revision, codes 162, 163) and 61 matched controls for differences in exposure to curing process.

An association between bronchogenic cancer and the tire-curing process has recently been reported in the above-mentioned study of British rubber workers.[15] Although the four individual cohort SMRs for lung cancer were low, proportional mortality analyses at other plants within company A identified three plants with 50–100% proportional excesses of lung cancer deaths. From these three plants, 61 lung cancer cases were identified, and their work histories were compared with those of 61 controls, for differences in exposure to curing (as well as to tire-building, with which an association has also been recently reported*). Controls were matched on sex, race, age, and plant. Tire-building showed no association, but curing clearly did, both in terms of the numbers of cases and controls exposed and in terms of the average duration of exposure of those cases and controls who had worked in curing (see FIGURE 8). The pattern of current smoking habits by work area in another tire-manufacturing plant indicates that smoking was unlikely to have been a confounding factor in this analysis. (The association between lung cancer and curing becomes stronger when two of the nine exposed controls, first exposed less than ten years before death, are eliminated.) Replication of this study at other plants is under way.

In addition to the above-mentioned case-control studies of leukemia and lung cancer, each with a specific hypothesis testable in terms of recorded job exposures, exploratory analyses were carried out for the job exposure correlates of stomach, bladder, and prostate cancers, and lymphosarcoma and Hodgkin's disease. These preliminary analyses, done within company A. were based on a comparison of work-histories between each cause-of-death case group (e.g. all the stomach cancer deaths) and an age-stratified random sample comprising 23% of the cohort. Jobs in this particular plant were classified into 17 categories similar to those in FIGURE 6. Each case group was compared with the cohort sample for differences in the proportion that had spent two or more years in each job category. The results are summarized in TABLE 2.

Stomach cancer is associated with compounding and mixing, milling, and with jobs involving contact with "green rubber" (postmilling but precuring),

particularly tread extrusion. Monson and Nakano have recently made a preliminary observation within another major rubber company cohort, noting an excess of stomach cancer deaths among workers in the rubber "processing" division (which includes mixing, milling, and calendering).[11]

There is a distinct pattern of job associations for bladder cancer, with a considerably larger proportion of the cancer case group having spent two or more years in "raw ingredients"-contact jobs than the cohort sample. Five of the six work areas showing an association with bladder cancer are near the beginning of the production line: shipping and receiving, compounding, mixing, milling, and calendering. The likelihood of contact with carcinogenic raw-ingredient chemicals is high in these work areas. An association of bladder cancer with "shipping" has been reported elsewhere twice,[11] although it is not clear whether that job designation included the receiving and storage of raw chemicals.

Few associations are apparent for cancer of the prostate gland. However, the association with compounding and mixing is of interest, since this work area entails contact with metallic oxides (including cadmium oxides) that are used as vulcanization accelerators. Cadmium has previously been found to be associated with prostate cancer.[23]

No significant associations were observed for lymphosarcoma and Hodgkin's disease (for which there was an SMR of 169 in company A; see FIGURE 5). It must, however, be remembered that for each of the cancers included in TABLE 2, the work-history analysis was exploratory, and therefore used a general job classification scheme that may have been unrelated to the actual physical distribution of specific carcinogenic agents that might actually be responsible for these cancers. Further, the number of cases available from one plant is often too small for reliable conclusions (e.g. bladder cancer), and therefore these analyses are being repeated in other plants.

TABLE 2

ASSOCIATIONS OBSERVED BETWEEN STOMACH, PROSTATE, AND BLADDER CANCER AND EMPLOYMENT FOR TWO OR MORE YEARS IN VARIOUS JOB CATEGORIES: RESULTS OF PRELIMINARY ANALYSIS IN COMPANY A *

Cancer Site	Number of Cases	Associated Job Categories
Stomach	42	Compounding and mixing, milling, tread extrusion and cementing, tube and flap building, "green" tire preparation.
Prostate	56	Compounding and mixing, cement mixing, janitoring, and trucking.
Bladder	12	Receiving and shipping, compounding and mixing, cement mixing, milling, calendering, janitoring and trucking.

* Work histories of each cause-of-death case group were compared with those of an age-stratified sample (N=1476) of the cohort. The comparisons were age-adjusted.

SUMMARY

Several previous epidemiologic studies of the rubber industry—an industry that uses many chemicals—have identified excess mortality from certain specific cancers. In this study, four cohorts of active and retired workers, at four major rubber-tire plants. were identified historically and followed for the ten-year period from 1964 to 1973. The cancer mortality of these four populations was compared. separately and combined, with that of the general community. For all cancers combined, there was a slight excess above the expected number of deaths, whereas for some specific cancers (stomach, colon, prostate, and neoplasms of the lymphatic and hematopoietic system) there was a marked ex—— of deaths. Prbportional mortality analysis at other small plants revealed similar excesses for these cancers, and some excess for lung, bladder, and CNS cancers. Analysis of detailed individual work histories reveals an association of certain cancers with specific job exposures; in particular, lymphatic leukemia and solvent exposure, and lung cancer and curing-room exposure. For both bladder cancer and stomach cancer, preliminary analyses indicate an association with groups of jobs in adjacent production stages (handling and mixing raw ingredients, and processing the "green" precured rubber. respectively). Further analytic studies are currently under way to identify groups of rubber workers at increased risk of other specific cancers.

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