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In December 1977, University of North Carolina researchers prepared a report for the "The Joint URW-Goodyear Occupational Health Committee" titled "Lung Cancer Among Rubber Workers At the Goodyear Akron Plants: A Case-Control Study." This study discusses the then-existing knowledge of other risk factors for the development of lung cancer. With respect to the association between asbestos and lung cancer, the North Carolina researchers wrote, **"a causal association between occupational exposure to asbestos fibers and lung cancer and pleural mesothelioma has been well-demonstrated."** No evidence exists that Goodyear had ever disavowed in any manner this report prepared for, reviewed by, and presumably approved by and disseminated by the Goodyear Health Committee and Goodyear.

Significantly, this Goodyear report cites primarily to Selikoff and Churg's 1968 publication for this bolded proposition, and we can argue that Goodyear has acquiesced to the proposition that the link between asbestos and lung cancer and mesothelioma was established by 1968. Accordingly, we can argue that the jury can consider this adoptive admission as evidence showing that Goodyear should have warned users of its gasket material at least by 1968.....

LUNG CANCER AMONG RUBBER WORKERS AT THE GOODYEAR AKRON PLANTS: A CASE-CONTROL STUDY

Report Prepared for
The Joint URW-Goodyear Occupational Health Committee

by

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Elizabeth Sills Delzell. Lung Cancer Among Rubber Workers: A Case-Control Study. Under the direction of Dragana Andjelkovich and Herman Tyroler. The following report is an adaptation of the thesis submitted to the faculty of the University of North Carolina in partial fulfillment of the requirements for the degree of Master of Science in Public Health in the Department of Epidemiology.

SUMMARY

Previous assessments of the effects of work-related exposures in the rubber industry on lung cancer mortality have been inconclusive but suggest that an increase in lung cancer risk may be associated with the history of employment in certain work areas within the rubber industry. Specifically, workers with exposures to processes involving the compounding and mixing of raw materials and the curing of green rubber products have been shown by more than one independent study to sustain a greater than expected lung cancer mortality. These findings have not been consistent across all studies of mortality among rubber industry employees.

The main objective of the present study was to identify groups of rubber industry workers, categorized according to their work experience, who may be at increased risk of dying of lung cancer. In addition to evaluating the lung cancer risk associated with employment in the compounding and mixing and curing work areas, the present study sought to ascertain the extent of associations, if any, between lung cancer mortality and history of employment in other work areas.

A matched case-control study design was used to identify possible high risk work areas at an Akron, Ohio rubber plant. The detailed employment records of 121 white male lung cancer cases and 448 controls, matched on race, sex, year of birth, and year of first hire, were examined. Effect measures were estimated for 19 work areas. Mean durations of employment and mean years of first employment in each work area were also compared for cases and controls.

Results indicate that, for the population of rubber workers studied, there is no association between risk for lung cancer and history of employment in the Compounding and Mixing and Curing work areas. A statistically significant elevation in risk was detected for the Reclaim Operation work area, for those employed for 5 or more years. Furthermore, among cases and controls employed in Reclaim Operation for at least 1 month, cases worked for twice as long as controls, on the average, in this work area. Study findings also suggest that there may be weak associations between a history of employment in work areas designated as Chemicals, Pliofilm, and Special Products Manufacture. Further epidemiologic and environmental research is needed to identify specific respiratory system hazards, if any, in these work areas.

Information regarding cigarette consumption and several other known risk factors for lung cancer was not available for the subjects of the present study. Because it was not possible to control for the effects of these potential confounders, the results of this study should not be regarded as conclusive.

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the rubber industry is indicated, in order to clarify the interpretation of these results. Thus, it is the goal of the present investigation to identify sub-groups of workers who may be at high risk of lung cancer mortality by virtue of their employment experiences in the rubber industry. In order to obtain a valid evaluation of the possible association between rubber industry employment and lung cancer mortality, other known disease determinants that may also be related to job patterns within the rubber industry must be considered. These known correlates of or risk factors for lung cancer will be reviewed in Chapter II.

CHAPTER II

LITERATURE REVIEW

A. Descriptive Epidemiology and General Risk Factors

1. Extent of the Problem

Lung cancer[1], as a cause of cancer death in the United States, ranked first among males and fourth among females in 1969 and accounted for approximately 75,000 deaths in 1974 (11,12). For the latter year, estimates based on the Third National Cancer Survey indicated that there were 83,000 new cases of lung cancer in the United States (11). Lung cancer is a rapidly fatal disease, with a 5-year survival for all stages of 8% for males and 12% for females (1). Thus, mortality data for lung cancer yield conservative but not greatly distorted estimates of the incidence and impact of lung cancer. In 1967, the following age-adjusted mortality rates per 100,000 for cancers of the lung, bronchus, and trachea were noted (13)[2]: 19.7 for white males; 22.1 for nonwhite males; 2.9 for both white and nonwhite females. The rates are applicable to cancers of the lung, bronchus, and trachea that were designated as primary. Mortality rates that combine lung cancers specified as primary with those

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[1]The terms "lung cancer" and "cancer of the lung" used in this paper refer to all cancers of the lung, bronchus, and trachea, International Classification of Disease (ICD) (Eighth Revision) #162, unless otherwise stated.

[2]Directly adjusted, using the 1960 U.S. population as a standard.

unspecified as primary or secondary are considerably higher: for example, 49 per 100,000 for white males and 54 per 100,000 for nonwhite males.

Murray and Axtell (14), using U.S. Vital Statistics data for 1968, calculated work-years lost due to lung cancer deaths based on life expectancy coverage for the working years included in the age interval of 20-65 years. It was estimated that lung cancer deaths in 1968 accounted for 222,948 lost work-years for white males and thus had the greatest impact on the male labor force of all cancer causes of death. It is apparent that lung cancer has a substantial impact on both the general and working populations in this country in terms of overall mortality and work years lost.

2. Trends Over Time in Lung Cancer Mortality

Lung cancer mortality rates rose rapidly for all race-sex groups between 1950 and 1967 in the U.S. (13). Figures for other countries indicate that this increase over time has been consistent in all parts of the world studied (15). For the U.S., the age-adjusted lung cancer mortality rates for white males and females and for nonwhite females more than doubled between 1950 and 1967, and a three-fold increase was sustained by black males during the same time period (16). Higgins (17) examined 1940 through 1967 time trends in age-specific respiratory cancer mortality rates and reported increases for ages 35-74 for all race and sex groups. Among U.S. white males, ages 35-44, lung cancer mortality rates increased at a constant rate between 1940 and 1967, while in the three older 10-year age groups, lung cancer mortality rates increased at a declining rate.

The age differential in the rate of increase noted by Higgins may be indicative of either additional or higher dose exposure for the

younger age groups or of relatively earlier exposure to carcinogenic or promoting agents. Higgins also reported that, in England and Wales, lung cancer mortality rate per 100,000 increased from 39.08 in 1950 to 67.72 in 1964 for males and from 5.8 to 9.7 for females. The comparable figures for the U.S. white population are, for males, 18.44 in 1950 and 36.86 in 1964 and, for females, 3.83 in 1950 and 5.83 in 1964. These changes correspond to the following percent increases in lung cancer mortality rates: in England and Wales, 73.3% for males and 67.2% for females; in the U.S., 99.9% for males and 52.2% for females. It should be noted that the difference between England and Wales and the U.S. in the percent change in male rates--73.3% compared to 99.9%--may be partially accounted for by the fact that the U.S. rate in 1950 was lower than the rate for England and Wales in 1950, and, consequently, a smaller absolute increase in the U.S. lung cancer rate over the 14-year time period produced a larger percent change. However, for both countries, the observed temporal trends probably reflect changes in the prevalence of environmental agents that have an impact on lung cancer development and, in particular, change in tobacco consumption habits, occupational exposure patterns, and urban air pollution levels.

3. Geographical Variation

According to estimates for 1966-67, lung cancer mortality rates show extensive geographical variation (15). In general, rates are highest in the highly industrialized countries of northern Western Europe and relatively low in Southern Europe (Italy and Portugal), Japan, and Chile. However, lung cancer rates may exhibit considerable variation within such geographical regions. For example, while Finnish males had a high

age-adjusted lung cancer death rate in 1966 through 1967 (61 per 100,000), Norwegian males had the third lowest rate among 25 countries (14.9 per 100,000).

In a rank ordering of lung cancer mortality rates among males for 25 countries (15), England and Wales were ranked highest, the U.S. ranked ninth and tenth for nonwhites and whites respectively, and Portugal was ranked lowest. A greater than seven-fold variation in rates between the lowest and highest ranked countries was noted. Doll (18), using approximate cumulative incidence rates, estimated a world-wide range in risk of developing lung cancer for populations under 75 years of age. He reported that this risk was 11% in England, while for Nigeria, it was 0.1%--a 100-fold variation. This estimate must be viewed with caution, since the cumulative incidence (risk) for Nigeria may be underestimated because of inaccurate or incomplete disease reporting practices.

Some of the observed variability in lung cancer mortality rates between the sexes within a given country and among various countries within larger geographical groupings may certainly be attributable to differences in completeness of lung cancer detection and diagnosis and, possibly, in enumeration of the population-at-risk forming the denominator of the rates. However, geographical variation may also reflect differences in exposure to lung carcinogens, in competing causes of mortality, or in host susceptibility.

Geographical variation in lung cancer mortality patterns is also apparent within the U.S. (19). For white males, areas having age-adjusted rates that are significantly high compared to the U.S. as a whole include urban regions in the Northeast; parts of Texas, Louisiana, Mississippi, Alabama, and Florida that border the Gulf of Mexico; and parts of eastern

Florida, Georgia, and South Carolina that lie along the Atlantic Coast. This pattern is similar, although less pronounced, for white females. The geographical variation in lung cancer mortality in the U.S. may be partially attributed to effects of urban air pollution and to differences in employment in heavy industry and in consumption of cigarettes. The explanation for the high lung cancer death rates experienced in the Gulf of Mexico and southern Atlantic coast regions is obscure. However, a recent study by Blot and Fraumeni (20) suggests that the presence in these areas of petroleum, ship building, and paper industries is correlated with higher than expected lung cancer death rates for both white and nonwhite males. Employment in these industries may involve exposure to lung cancer hazards.

4. Age

Cross-sectional analyses of age-specific lung cancer death rates indicate that rates for males increase for each five-year age interval after the age of 35, up to age 70, then decline rapidly (21-23). The age curve for females does not exhibit this pattern: rates for females increase steadily with age, up to the oldest ages, and the rate of increase is much less for females than for males. When analyses of male lung cancer death rates by birth cohort are performed, it is apparent that both male and female rates increase with each increment in age. Furthermore, each successive birth cohort experiences a higher lung cancer death rate. Thus, at a given age-at-death, the rates increase for each birth-year cohort. This cohort effect has been ascribed to intensified smoking among successive birth cohorts.

5. Sex

Lung cancer incidence and mortality rates for males are consistently higher than female rates in the U.S. and in other countries studied (13,15,24). Cancer morbidity surveys in the United States indicated that male lung cancer rates for both whites and nonwhites were approximately three times higher than rates among females in 1937, 4.5 times higher in 1947, and about 5 times higher in 1969. Comparisons of age-adjusted lung cancer mortality rates for the years 1950-1967 reveal that sex ratios increased for whites and nonwhites through 1960. Since 1960, sex ratios have been decreasing steadily. This decrease is due to a greater percent change in lung cancer death rates for females than for males during this time period.

The lower lung cancer rates observed among females may be attributable to several factors. Among these are male/female differences in occupational exposure to respiratory system hazards and in cigarette smoking habits; it has been suggested that females smoke fewer cigarettes, inhale less intensely, and begin smoking at later ages than males (25).

6. Race and Ethnicity

Prior to 1960, lung cancer mortality rates in the U.S. for nonwhite males and females were below those for whites. In 1960 and in subsequent years, nonwhite rates have been higher than rates among whites (13). In 1969, lung cancer incidence was 84.7 per 100,000 for nonwhite males, compared to 68.9 per 100,000 for white males. The corresponding rates per 100,000 for females were 18.2 for nonwhites and 13.5 for whites. It is apparent that the race differential is greater for males than for females, possibly reflecting greater differences in exposure to carcinogens and/or in susceptibility among nonwhite compared to white males

than among nonwhite compared to white females.

Several other ethnic groups in the U.S. have lung cancer mortality experiences that differ from that of the general U.S. population. Fraumeni and Mason (26) evaluated lung cancer mortality among Chinese Americans. Their analysis was based on death certificates obtained for the years 1950-1969 and Census information for 1950, 1960, and 1970. They determined that age-adjusted lung cancer death rates were significantly higher for both male and female Chinese Americans than for both the general white and nonwhite populations of the U.S. The excess was greatest for Chinese American females. The magnitude of this excess--twofold for females--is not large and may have resulted partly from underenumeration by the Census of the Chinese American population. Fraumeni and Mason were unable to differentiate between immigrant and U.S.-born Chinese. Also, no information on cigarette smoking habits of the Chinese Americans was available. Therefore, it is difficult to interpret the results of this study.

Creagan and Fraumeni (27) studied the 1950-1967 cancer mortality among American Indians, again using death certificates and Census information. Comparisons of observed numbers of lung cancer deaths with expected numbers based on the lung cancer mortality experience of the general U.S. population indicated a substantial deficit of lung cancer among both male and female Indians. The authors suggested that differences in cigarette smoking between Indians and the general U.S. population might have accounted for the observed deficit.

Finally, Buell, et al. (28) identified an excess in lung cancer mortality among female Mexican immigrants in the U.S. The observed excess was largely confined to those who had spent their early life in

Mexico and was ascribed by the investigators to heavy cigarette smoking by these women.

7. Urban Environment

Numerous studies carried out in Great Britain and the U.S. indicate that lung cancer mortality rates are higher in urban than in rural areas (29-34). The lung cancer excess observed in urban areas has been attributed partially to the higher degree of air pollution found in the urban environment. Interpretation of the findings of these studies has been hindered by lack of or poor quality of information pertaining to tobacco consumption, changes in residence, and environmental measurements. However, several studies of lung cancer mortality have examined both place of residence and smoking habits of study subjects (30-32). Results consistently indicate that at each level of smoking, age-adjusted lung cancer death rates are higher for residents of urban areas and that the urban effect is greatest among nonsmokers.

For example, in a prospective study of 187,783 U.S. white males followed between 1952 and 1955, Hammond and Horn reported the following results: a) age-adjusted lung cancer mortality rates per 100,000 among nonsmokers increased from 4.7 for residents of towns having a population of fewer than 10,000 to 14.7 for residents of cities having a population in excess of 50,000; and b) for smokers, rates increased from 71.7 to 85.4 per 100,000 over the same population gradient. In 1958, Haenszel and his coworkers (30) were able to collect data on both smoking habits and duration of residence for 2,191 white male lung cancer deaths occurring during that year and for a representative national population sample of approximately 30,000 white males, ages 35 and over. They found

that the lung cancer excess for residents of urban versus rural areas increased with duration of residence. Furthermore, among lifetime residents of urban or rural areas, the excess in lung cancer mortality for urban residents was present for every smoking category and was greatest for non-smokers and smallest for smokers of more than one pack per day. Neither of the above-mentioned studies was able to take occupation of study subjects into account.

Hammond (35) reported the results of a study of 1,000,000 men and women in 25 states followed prospectively for six years, starting in 1959. Information on smoking habits, place of residence, and occupation was collected. In order to evaluate the effects of urban residence, Hammond confined analyses to male subjects who had lived for at least ten years in their place of residence at the beginning of the study. Age and smoking-adjusted lung cancer mortality rates were calculated for men occupationally exposed and not occupationally exposed to dusts, fumes, vapors, gases, or X-rays, separately for urban and non-urban residents. Results indicated that, when occupational exposure to respiratory hazards was taken into consideration, only slight residual differences in lung cancer mortality attributable to urban versus rural residence were detectable. This study emphasizes the importance of controlling not only for smoking and age, but also for occupation, when examining the association between urban residence and lung cancer mortality.

The effects of urban air pollution on lung cancer occurrence remain unclear. If the association is real, its strength is clearly much smaller than that of the relationship between lung cancer and smoking. Several studies (33,34) have indicated that the effect of urban residence is considerably less in females than in males. Although these studies did

not control for smoking, this observation provides additional evidence for Hammond's suggestion that urban/rural variation in lung cancer mortality may be due to occupational factors.

8. Migration and Nativity

Studies of the cancer experience among migrants are of interest, since they potentially provide a means of determining whether environmental or genetic factors predominate in the etiology of a given cancer. Mortality rates for cancers whose development is influenced by environmental factors will assume a level for migrants that is intermediate between the death rate in the country of origin and that in the country of destination, reflecting the influence of environmental factors present both in early life, prior to migration, and in subsequent time periods (36).

In general, lung cancer death rates for migrants are intermediate between the rates in their new and former countries (37). This has been demonstrated for British migrants to South Africa (38). Lung cancer mortality rates of native-born residents of South Africa, British-born residents of Great Britain, and British immigrants to South Africa were compared. The rate for immigrants was intermediate between the high British rate and the lower South African rate. No evidence for a relatively decreased amount of smoking among British migrants could be found to account for their lowered (in comparison to British rate) lung cancer rate.

Reid et al. (39) compared the rates of Norwegian and British immigrants to the U.S. with rates for the native-born U.S., Norwegian, and British populations. 1960-62 rates for Norway and Britain and 1959-61 rates for the U.S. were used for these comparisons. For the British immigrants, age-adjusted lung cancer death rates were higher than U.S.

rates and lower than British rates. Lung cancer mortality rates in Norway were lower than in the U.S. Norwegian immigrants were shown to have lung cancer mortality rates higher than the Norwegian rates but lower than the U.S. rates.

Haenszel (37), using all lung cancer deaths occurring in 35 states in 1950, found intermediate rates for male migrants from Italy, Germany, Sweden, Norway, and England and Wales. No consistent pattern was observed for females, and no cigarette consumption data were available.

Mancuso (40) compared the 1947-51 lung cancer mortality experience of male foreign migrants to Ohio with that of white males in Ohio. Again, intermediate rates for German, British, and Italian male immigrants were reported.

The effects of migration within the U.S. on lung cancer mortality have also been evaluated. Haenszel (30) demonstrated an excess in lung cancer mortality for white males who had moved from rural to urban areas in the U.S. Mancuso (41) analyzed the mortality experience of migrants to Ohio. The study included all deaths reported for Ohio residents dying in the U.S. and Canada between 1959 and 1968. Directly age-adjusted rates were computed, using the 1960 general U.S. population as the standard. Lung cancer death rates were found to be higher than rates for native born Ohio residents in the following groups: a) white male and female residents of Ohio who were born in the South or the Northeast; b) non-white male and female residents of Ohio who were born in the South or Northeast. The differences between lung cancer death rates for migrants and those for native-born Ohioans were greater for males than for females and were particularly striking for non-white males.

The observed differences in lung cancer mortality between migrants from the Northeast and native Ohioans suggest that environmental factors present in early life influenced the subsequent mortality experience of migrants from the Northeast, since this region has a high lung cancer death rate. However, lung cancer mortality rates in much of the South are lower than in the U.S. and are not significantly different from rates in most of Ohio. Mancuso suggests that the unfavorable lung cancer mortality experience of migrants to Ohio from the South may be attributable to the differential employment of migrants in hazardous occupations and heavy industrial settings. However, other explanations for the apparent elevated lung cancer mortality among the southern migrants cannot be ruled out. The possibility exists that individuals migrating from the South to Ohio were more heavily exposed to environmental carcinogens in their native southern states than either the population remaining in the South or the native Ohioans. In addition, if one assumes that economic deprivation provides the impetus for migration, it is possible that migrants, as a group, compared to native Ohioans, may be of lower social class, may be in poorer general health because of nutritional deficiences and lack of medical care experienced in their birth states, and may have less access to health care facilities and fewer social supports in their adopted state than do native Ohioans who do not emigrate. These factors may differentially influence the susceptibility of southern migrants to Ohio. Mancuso and other investigators have not considered the possible impact of these variables on the lung cancer mortality experience of migrants.

several studies have shown that lung cancer patients have higher levels of AHH inducibility than do normal controls (45-47). The possibility that AHH inducibility, as well as other genetic biochemical markers, may prove to be useful in identifying individuals who are at particularly high risk for lung cancer has been discussed recently by Mulvihill (48).

B. Occupational Factors

It is recognized that exposures to environmental carcinogens, promoters, and respiratory system irritants encountered in various occupational settings can substantially increase the risk for lung cancer among industrial workers, especially among those who smoke (3). A number of occupational lung cancer studies have provided assessments of the association between lung cancer mortality and work-related exposures. These studies, and occupational studies in general, have been hindered to varying degrees by lack of adequate data, as discussed below.

First, there are frequently insufficient numbers of employees-at-risk and employee deaths to yield stable risk estimates. Second, information pertaining to the smoking and demographic characteristics of the study population may not be obtained. Some of these factors may be major disease determinants and may, therefore, distort attempts to evaluate associations between occupational exposures and health consequences. The validity of findings may be seriously questioned when measurement and control of the effects of these potential confounders are neglected. Third, ascertainment of the population-at-risk, both exposed and unexposed, and of subsequent mortality may be incomplete.

Again, the validity of estimated effect measures derived from cohort studies may be challenged on the basis of this limitation.

Besides the problems of incomplete identification of workers-at-risk and attrition caused by unsuccessful attempts to trace the mortality experience of all study subjects, several additional factors that potentially lead to dilution of the estimated effects of exposure derived from studies of various occupational groups and that may contribute to great variation in effect measures over the relevant studies are often not considered. First, detailed employment information, permitting accurate assessment of exposure, is often unavailable. Lack of exposure information, in terms of qualitative and quantitative environmental measurements, as well as changes in exposures over time, may lead to misclassification of workers by exposure. This inability to distinguish between lightly and heavily exposed workers and the resulting misclassification of workers according to the exposure of interest may bias measures of effect towards the null. Furthermore, failure to take into account the possible effects of other or multiple exposures often present in complex industrial environments may restrict inferences that can be made regarding the causal nature of any observed association between the disease and the exposure of primary interest.

Second, adequate follow-up or lapsed amount of time between first exposure and initiation of the study to allow lung cancer or other cancers to occur may not be provided. As a consequence of this problem, the impact of the exposure on the health effect of interest is likely to be underestimated.

Provision of a sufficiently long follow-up period is partly dependent on accurate knowledge regarding the length of the latent

period or induction time of occupational lung cancers. Estimates of the latent period for lung cancer, based on the findings of epidemiologic studies, are extremely variable, as demonstrated in Table 1. Values in this table derive from the results of more than one study of each exposure mentioned. The fluctuations in estimated mean latent period and the width of the reported ranges may reflect both differences in methodology of detecting cases and determining exposures and variation in potency and dose of carcinogens constituting the "exposure" in each study situation. Lack of accurate knowledge of the induction times of lung cancers associated with work exposures prevents the exclusion of both irrelevant exposures and irrelevant cases and the identification of the time period during which exposures of etiologic significance could have taken place. An accurate calculation of effect measures, such as relative risk for exposed versus non-exposed subjects, is possible only when appropriate length of follow-up, taking latent period into account, has been provided and when irrelevant cases or exposures have been excluded.

Finally, when the occupational group of interest cannot be separated into exposed and unexposed subgroups, an external population must be sought in order to make comparisons and to derive estimates of effect of the exposure of interest. The magnitude of estimated effects may vary according to the particular population used for comparisons. Since working populations are usually healthier than a general population, choice of the general population of a country or a state as a comparison group may contribute to a dilution of the observed effects of exposure.

TABLE 1

LATENT PERIODS OF OCCUPATIONAL LUNG CANCERS

Agent	Average Latent Period (years)	Range of Latent Period (years)
Chromates	15	5-47
Nickel	22	6-30
Ionizing radiation	25-35	7-50
Asbestos	18	15-21
Tar Fumes	16	9-23
BCME (bis-chloromethyl ether)	15	10-24

SOURCES: Kotin, P. (Ref. #36)
Weiss, W. and Figueroa, W.G. (Ref. #73)

Because of the above-mentioned and other limitations, the findings of occupational lung cancer mortality studies should be interpreted with caution. The results of a number of such studies will be reviewed below. First, findings regarding lung cancer mortality in industries involving exposure to inorganic substances will be discussed. These industries include the following: chromate production and processing, nickel refining, cadmium smeltering, copper smeltering, lead smeltering, iron ore mining, insulation and other work involving asbestos. Also included in this section will be uranium mining. Major findings relevant to the lung cancer mortality experience of workers in these occupations are presented in Table 2-a.

TABLE 2-a

OCCUPATIONAL LUNG CANCER:
INDUSTRIAL EXPOSURES TO
INORGANIC COMPOUNDS

Industry/Occupation	Suspected Agents	Experimental Data*	Estimated Magnitude of Excess	Reference #
Chromate Production & Processing (Pigments Industries)	lead chromate	+	SMR = 486-1865	49,50
	zinc chromate	+	SMR = 3800	52
			SMR = 350	51
Nickel Refining	Nickel Carbonyl	+	SMR = 130-1050	54
	other Ni compounds . . .	+	SMR = 600-800	55
Cadmium Smelter Workers	Cadmium oxide dusts . . .	+	SMR = 235-299 (for workers having 30+ years since first hire)	56
	Cadmium sulfate	+		
Copper Smeltering; Insecticide & Pesticide Producers & Users	Arsenic compounds . . . . (As_2O_3, Na arsenite, Pb arsenite)	-	SMR = 450-800 (for workers exposed 15+ years)	58
			SMR = 350	59
Lead Smelter & Battery Plant Operators	Various: Pb, As & Cd compounds; SO_2	+ (for Cd)	SMR = 148 (Smelters)	61
			SMR = 132 (battery plant)	61

TABLE 2-a, continued

Industry/Occupation	Suspected Agents	Experimental Data*	Estimated Magnitude of Excess	Reference
Iron Ore (Hematite) Miners	Iron Oxides	+	PMR = 174	63
	Radiation	+		
Asbestos Workers	Asbestos fibers	+	SMR = 760	64
			SMR = 417	65
Talc Miners & Millers	Talc dust (asbestos fibers)	+	PMR = 320	66
Uranium Miners	Radon daughters (^{214}Pb, ^{214}Po, ^{218}Po) . .	+	SMR = 900	68,69

* A "+" indicates that results of experimental tests are positive for the agent of interest; a "-" indicates negative results.

Taylor and his co-workers (49,50) studied the mortality experience of 1,213 male chromate workers at three plants. The study population consisted of workers who were employed between 1937 and 1940. Not all workers employed prior to 1937 were included in this investigation. The follow-up period for subsequent mortality among the workers was approximately twenty years, through 1960. There were 71 respiratory cancer deaths. Standardardized Mortality Ratios (SMR's), with expected numbers of deaths calculated on the basis of U.S. male rates, were 468 for workers employed between 1937 and 1940 and 1864.5 for those first employed between 1941 and 1945, indicating an approximately 4.5- to 18.5-fold excess for these workers.

Bidstrup and Case surveyed 724 British chromate workers employed at three plants in 1949 (51). Seven hundred twenty-three were found to be free of lung cancer and were followed for approximately 5.5 years, through August, 1955. There were 12 lung cancer deaths, compared to 3.3 expected, based on the mortality experience of the male population of England and Wales. Thus, the SMR was 350. Furthermore, for seven (58%) of the deaths, the age at death was less than 55. It is unusual to find this large a proportion of young decedents among a group of lung cancer deaths.

Langard and Norseth (52) studied 24 workers who had been employed for at least three years in a Norwegian chromate pigment producing plant and noted an excess in lung cancer mortality. However, their observation was based on only three lung cancer cases.

Lead, zinc, and calcium chromate have been found to be carcinogenic experimentally (53). In addition, these compounds are pulmonary irritants. The lung cancer risk for users of chromate-containing pigments has not yet been evaluated.

Doll (54) followed the mortality experience of 845 nickel refinery workers, having at least five years of employment and first employed prior to 1945, from 1939 through 1966. Annual age- and cause-specific rates for the population of England and Wales were applied to the man-years at risk of the workers to derive SMR's. SMR's for those first employed before 1925 were approximately 950, while for workers first employed after 1925, the SMR was 130. Nickel carbonyl, which has been found to be a pulmonary carcinogen in rats, was manufactured at the plant both before and after 1925. The authors concluded that nickel carbonyl was not solely responsible for the excess in lung cancer deaths among the refinery workers. Other nickel compounds, alone or in combination with arsenic present as an impurity in the refining process prior to 1925, may have contributed to the observed elevated lung cancer mortality.

Pederson (55) investigated 1,916 Norwegian nickel refinery workers who had first been employed before 1961 and who had worked in the refinery for at least three years. This population was followed from 1953 through 1971. Expected numbers of deaths were calculated on the basis of national age- and calendar-year-specific rates. SMR's for various jobs were 600-800. The greatest excess (SMR=1000) was experienced by workers first employed before 1945. In 1950, production changes that may have influenced exposures within the refinery took place.

There is some evidence that cadmium smelter workers may also be at increased risk for lung cancer, compared to the general population. Lemen et al.(56) followed 292 white male cadmium smelter workers, having a minimum of two years of employment and first employed between

1940 and 1969, through 1973. Their SMR for lung cancer was 235. This SMR is based on only two observed deaths and cannot be regarded as strong support for the hypothesis that cadmium exposure increases the risk for lung cancer. Arsenic, zinc, lead, and copper were also present as impurities in the cadmium smelter operations.

Copper smelter workers have been found to have excessive lung cancer. It is thought that the observed lung cancer excess may be caused by exposure to arsenic, and nine out of eleven epidemiologic studies of lung cancer mortality and exposure to arsenicals via smeltering and formulation and use of pesticides and insecticides containing arsenic have provided support for this hypothesis (57).

Lee and Fraumeni (58) compared the 1938-63 mortality experience of 8,047 white male smelter workers exposed to arsenic trioxide with that of a referent group consisting of the white male population residing in the same geographical region. Significant excesses in lung cancer mortality among smelter workers were detected for each duration of employment category. Rates more than 4.5 times higher than expected were observed for workers employed for at least 15 years, with the 15th year completed before 1938. Work areas within the smelter were grouped according to intensity of exposure to arsenic into heavy, medium, and light exposure areas. An SMR of 800 was observed for workers most heavily exposed and employed for 15 years or more. Dose-response for degree of arsenic exposure was observed in every duration of exposure category. Lee and Fraumeni stated that the eight-fold excess in lung cancer mortality observed among heavily exposed workers could not be accounted for by an unusually high prevalence of smoking. They cited as support for this conclusion the fact that age-adjusted death rates

for lung cancer among U.S. males for 1960-63 indicated a maximum 2- to 2-1/2-fold excess in rates for heavy smokers compared to the general population. The results of this study, although suggestive of an association between exposure to arsenic and development of lung cancer, may be challenged on the basis of lack of cigarette smoking information and presence in the work environment of other chemicals, especially sulfur dioxide, a lung irritant that may have an impact on lung cancer.

Ott et al. (59) reconstructed a cohort of 603 male workers who had been engaged in the production of arsenic-containing pesticides. The 1940-73 mortality experience of these workers was determined for 10-year age groups and 5-year calendar periods and compared with expected respiratory cancer mortality derived from the corresponding U.S. white male population. Results from this retrospective cohort analysis revealed an SMR of 3.45, which represents an almost 3-1/2-fold increase in observed over expected lung cancer mortality for workers with arsenic exposure. A cross-sectional review of smoking habits of workers exposed to arsenic carried out in 1968-72 indicated no differences in cigarette consumption related to degree of exposure. Ott and his co-investigators concluded that the role of arsenic in respiratory cancer development may be causal; however, it should be noted that their analysis is based on a small number of observed respiratory cancer cases (N=20).

Milham (60) conducted a retrospective cohort study of workers employed in a copper smelter that produced arsenic trioxide. The workers were followed for the period 1950-71, and 40 lung cancer deaths were detected, compared to 18 expected. The SMR was 222, indicating a 2-fold excess in lung cancer mortality for the smelter workers.

As previously mentioned, there have been 11 studies of various groups of workers exposed to arsenicals. Nine of these studies have indicated an association between lung cancer mortality and exposure to arsenic compounds. The studies by Ott et al. and Lee and Fraumeni demonstrated a dose response relationship between exposure and subsequent lung cancer mortality.

A retrospective cohort study was recently conducted to evaluate the mortality experience of a group of lead smelter and battery plant operators (61). Seven thousand thirty-two workers who had been employed for at least one year in the lead production industry were identified, and their mortality experience from 1946 through 1970 was ascertained. Lung cancer SMR's, with expected numbers based on the U.S. male population, were 148 for smelter workers and 132 for battery plant operators. In addition to lead these workers were exposed to arsenic, cadmium, and sulfur dioxide. Again, the complexity of the work environment makes it difficult to assess the effects of any one agent on lung cancer among the workers exposed.

It has been demonstrated experimentally that ferric oxide enhances the response to carcinogens in vivo: Ferric oxide (Fe_2O_3) is not itself a carcinogen. Rather, it acts as a vehicle for an absorbed carcinogen and increases retention of the carcinogen in the respiratory passages of experimental animals (62). Iron ore miners are exposed to Fe_2O_3, and there is some indication that they may have an elevated lung cancer mortality risk. Boyd et al.(63) examined 5,811 death certificates of British hematite (iron ore) miners. The deaths included in the study occurred between 1948 and 1967. The proportional mortality ratio (PMR) for lung cancer was 174 for underground miners, based on 36 observed

lung cancer deaths. This represents a 74% excess in the proportion of lung cancer deaths among all deaths for the miners. Radiation, which is known to have carcinogenic activity, was also present in the underground mine environment. Thus, the observed excess of lung cancer deaths cannot be ascribed only to exposure to iron ore dusts on the basis of findings presented in this study.

A causal association between occupational exposure to asbestos fibers and lung cancer and pleural mesothelioma has been well demonstrated (64,65). Selikoff (65) reported the lung cancer mortality experience of 17,800 asbestos insulation workers for the period 1967-72. He found a nearly 5-fold excess in observed deaths compared to expected deaths calculated on the basis of U.S. age-specific white male death rate data. The greatest excess (7-fold) was observed among workers having 30-34 years between year of first exposure and year of death. In another study, Selikoff and his co-workers (64) followed 370 asbestos workers with a minimum of twenty years of exposure to asbestos for 52 months (1963-67). Taking cigarette smoking habits and age into account, they found that asbestos workers' risk of dying from lung cancer was 7.6 times higher than expected. When asbestos workers who also smoked were compared to non-smokers not having previous exposure to asbestos, a 92 times higher than expected risk was estimated, suggesting multiplication of the effects of cigarette smoking and asbestos exposure.

Nicholson (65) studied the 1959-71 mortality of 689 asbestos production and textile workers. The study population consisted of workers who were current employees in 1959 and who had first been hired before 1939. The SMR, based on 27 deaths, for this group was 333.

Talc is a mineral that contains, in varying amounts, both free silica, which is a cause of pulmonary fibrosis, and different forms of asbestos. There have been conflicting reports in the literature regarding the possibility of increased lung cancer risk among workers engaged in talc mining and milling, as discussed below.

Kleinfeld, et al.(66), identified 260 talc workers who were current employees in 1940 and had worked for at least 15 years or who accumulated this amount of work experience between 1940 and 1969. Twelve cancers of the lung were observed during the follow-up period, compared to 3.7 expected on the basis of the proportion of all deaths due to lung cancer for the U.S. white male population in 1955. Thus, the Proportional Mortality Ratio of 3.2 indicated that the proportion of deaths due to lung cancer was slightly more than three times higher than expected for talc workers.

In contrast, Rubino, et al.(67) found no excess in lung cancer among Italian talc miners and millers. One thousand five hundred fourteen miners and 478 millers who began work in 1921 through 1950 and who had at least one year of work experience involving exposure to talc were studied. Follow-up for this group was conducted through June, 1974.

It is difficult to compare the findings of these two studies because of differences in minimum duration of employment criteria. The talc workers studied by Kleinfeld et al. were probably more heavily exposed, since they had to have worked for at least 15 years to have been included in the study. Furthermore, the type of talc to which workers were exposed was not the same for both studies. While the talc workers studied by Kleinfeld et al. were exposed to industrial talc containing relatively large amounts of free silica and asbestos, the

Italian miners and millers worked with very pure talc used in pharmaceutical and cosmetic industries. Thus, differences in study design and in the nature of qualitative and quantitative exposures may account for the inconsistent findings with respect to lung cancer mortality among talc workers.

Radiation is considered a physical, rather than chemical, carcinogen. The association between radon daughter exposure and subsequent respiratory cancer mortality was examined in a cohort study of 3,366 white male Uranium miners, conducted between 1957 and 1968 (68). Cumulative exposure to radiation was measured in terms of Working Level Month (WLM), a unit reflecting both intensity and duration of exposure. Excesses in respiratory cancer mortality for Uranium miners compared to white males of the same geographical region were detected for every cumulative exposure level higher than 120 WLM. Further examination of a subset of these miners, followed prospectively from 1964 through 1967, revealed respiratory cancer mortality rates among smoking miners that were approximately nine times the rates observed in a non-mining population with similar smoking habits during the same time period (69).

Workers occupationally exposed to certain organic compounds have been shown to experience an elevated risk for lung cancer. Among these high risk industries are the following: poison gas producers, ion exchange resin manufacturers, synthetic rubber and plastic producers, coal carbonization workers, and roofers. Epidemiologic studies examining the association between employment experience in these occupations and lung cancer mortality are summarized in Table 2-b, and will be reviewed below.

TABLE 2-b

OCCUPATIONAL LUNG CANCER:
INDUSTRIAL EXPOSURES TO
ORGANIC COMPOUNDS

Industry/Occupation	Suspected Agents	Experimental Data*	Estimated Magnitude of Excess	Reference #
Poison Gas Producers; Military	Mustard gas (ββ´-dichlorodiethyl sulfide)	+	SMR = 3667	70
Ion Exchange Resin Manufacturers	BCME	+	CIR¢ = 8	72,73
Synthetic Rubber & Plastics Production	Vinyl chloride	+	SMR = 156 SMR = 135	74 75
Bituminous Coal Carbonization Workers:	Polycyclic aromatic hydrocarbons (coal tars).	+	SMR = 252 (total coke oven) SMR = 1000 (coke oven, topside for 5+ years	76 76
Coke oven workers & gas producers (retort workers)			SMR = 3000 (Japanese gas workers) SMR = 180	79 77,78

* A "+" indicates that results of experimental tests are positive for agent of interest; a "-" indicates negative results.

¢ Cumulative incidence ratio.

Wada et al. (70) identified 2,620 former employees of a poison gas factory operated between 1925 and 1945 in Japan. Four hundred ninety-five of these workers were known to have manufactured mustard gas, ββ'-dichlorodiethyl sulfide. Deaths for the years 1952-67 were ascertained, and 33 deaths from respiratory cancer were observed among exposed employees. The expected number for 1952-67, based on Japanese national mortality rates for males, was 0.9. Thus, the SMR of 3,667 indicated a very large excess in lung cancer mortality for workers who were exposed to mustard gas. Not all former employees were included in the cohort of exposed workers, since it was estimated that approximately 5000 workers had been employed in the past at the plant. However, it is unlikely that the lung cancer mortality experience of the excluded workers was sufficiently lower than that of the workers included in the study to reverse the conclusion derived from the study that exposure to mustard gas was responsible for the excessive lung cancer mortality observed. It should be noted that the workers were exposed to other gases that are strong pulmonary irritants.

Workers involved in the manufacture of ion exchange resins constitute the principal group exposed to chloromethyl-methyl ether (CMME) and its frequent contaminant, bis-chloromethyl ether (BCME). BCME has been shown experimentally to be a potent pulmonary carcinogen (71). There is also epidemiologic evidence indicating that BCME is a strong lung carcinogen in workers exposed to this chemical. Figueroa et al. (72) followed 125 chemical plant workers, some of whom were exposed to BCME, between 1962 and 1972. Four lung cancer cases occurred during the first five years of follow-up, resulting in a five-year incidence of 4.54%. This result was compared to the incidence of lung cancer in a

referent group having a similar age distribution and not exposed to CMME or BCME. The five-year incidence for the latter group was 0.57%. The ratio of the incidence in the exposed to that in the unexposed is 9.24, indicating a 9-fold excess in lung cancer for the exposed workers. The 10-year follow-up for the same group of workers confirmed a high lung cancer incidence among those exposed to BCME (73). For the entire 10 year period, there were 16 deaths; 11 of these were due to lung cancer; and all lung cancer deaths occurred among men who were less than 55 years of age. Furthermore, the smoking habits of the study subjects were evaluated. An inverse relationship between amount of tobacco smoked and lung cancer incidence was observed. Since the authors made no attempt to identify and trace workers who may have been exposed to BCME and who may have terminated their employment prior to the initiation of the study, the possibility that selective transfer out of the industry by heavy smokers who were exposed to BCME may have occurred cannot be ruled out. Such selection may have influenced the results of the study.

A retrospective cohort study by Waxweiler et al. (74) examined the mortality experience of 1,294 workers who had been engaged in the polymerization of vinyl chloride. The lung cancer SMR reported was 156, based on 12 observed lung cancer deaths. Tabershaw and Gaffey (75) reported an SMR of 135 for a subset of highly exposed vinyl chloride workers. The results of these studies suggest that vinyl chloride exposure may be associated with an increased risk for lung cancer.

Excesses in respiratory cancer have been reported for coal carbonization workers: specifically, for coke oven workers in the U.S. steel industry (76), for retort workers in Great Britain (77,78), and for gas generator workers in Japan (79).

Kawai et al, (79) carried out an investigation of the mortality experienced by gas generator workers at a Japanese steel plant. The cohort of interest had worked at the plant until it was closed in 1953 and consisted of 504 male workers. 25,760 other steel workers comprised the comparison group. During the follow-up period (1953-65), six lung cancer deaths were detected, compared to 0.18 expected. It is difficult to make conclusions regarding the strength of the association between exposure to coal carbonization products and lung cancer, based on the findings of this study, because of the small numbers of observed and expected deaths. However, the results of Lloyd's study and Doll's studies, in addition to those reported by Kawai et al., appear to give ample support to the hypothesis that exposure to polycyclic aromatic hydrocarbons produced during the coal carbonization process increases lung cancer risks.

C. Lung Cancer Findings in the Rubber Industry

Occupational exposures to hazardous respirable organic and inorganic particulates have been shown to increase lung cancer mortality among exposed populations. Substances that may be potentially harmful to the respiratory system are or have been encountered in the occupational environment in the rubber industry. These materials have at some times included known lung carcinogens, such as lead chromate, which is used in pigments, and cadmium compounds, which have been used as accelerators in the vulcanizing process; lung irritants, such as carbon black, zinc oxides, and talc (which may contain varying amounts of asbestos - a known carcinogen); and tumor promoters, such as phenols.

Several early studies of occupational mortality in the U.S.. reported findings that include considerations of the rubber industry. In 1961-63, a national study of cause-specific mortality in 1950 and occupation as recorded on death certificates noted an excess of respiratory cancer for employees of the rubber industry (80). In 1967, a study of disability insurance benefits awards made between 1959 and 1962 to male workers under the age of 65 reported an excess in respiratory cancers for rubber industry employees (81). Since then, several studies of mortality in the British and U.S. rubber industries have been reported in the literature. Table 3 provides a description of the populations of rubber workers studied and a summary of the major findings, relevant to lung cancer, of these investigations.

Fox et al. (4,5) examined the mortality experience of 40,867 rubber workers in Great Britain between 1967 and 1971 and 1972-74. The study population was defined as all male workers at 381 firms identified by a 1967 census of the British rubber industry. All workers included in the study had to have had at least one year of employment at the beginning of the study. SMR's were computed using annual age- and cause-specific rates of the male population of England and Wales. For 1967-71, the overall lung cancer SMR was 119. For the tire manufacturing sector of the industry the SMR was 134, and the SMR for the sector designated as "Belting, hose rubber with asbestos, flooring," was 164. Lung cancer SMR's for the period of 1972 through 1974 were 118 for the overall industry, 128 for the tire manufacturing sector, and 106 for belting, hose rubber, and flooring. Thus, there was an excess in lung cancer mortality for the industry as a whole and for the tire sector for both follow-up periods.

TABLE 3

LUNG CANCER MORTALITY IN
THE U.S. AND BRITISH RUBBER INDUSTRIES:
OVERALL FINDINGS

Investigators¢	Period of Observation	N of Workers Studied	Standard Population	Estimated Effect #
Fox, et al. (1974)(4)			1967-70 male population	
Total Industry	1967-71	40,867	of England and Wales	SMR=119 (304)
Tire Manufacturing	"	16,035	"	SMR=134 (131)
Belting, Hose Rubber, and Flooring	"	4,350	"	SMR=164 (42)
Fox & Collier (1976)(5)			1967-73 male population	
Total	1972-74	40,867	of England & Wales	SMR=118 (281)
Tire Manufacturing	"	16,035	"	SMR=128 (117)
Belting, Hose Rubber, and Flooring	"	4,350	"	SMR=106 (25)
McMichael, et al. (1974)(82)				
Akron Plant	1964-72	6,678	1968 U.S. male population	SMR= 84 (91)
Plant B	"	108*	"	SPMR=169 (11)
Plant C	"	265*	"	SPMR=153 (17)
Plant D	"	189*	"	SPMR=229 (37)
Andjelkovich, et al.(1976)(83)	1964-73	8,418	1968 U.S. white male population	SMR= 80 (120)
Monson, et al. (1976)(8)				
Retrospective Cohort	1940-74	13,571	1940-69 U.S. white males	SMR= 92 (234)
Rubber Worker Deaths, Proportional Mortality	1925-39	688*	1925-39 U.S. white males	SPMR=140 (6)

¢ References are noted in parentheses, following date of study publication.
The number of observed lung cancer deaths is given in parentheses.
* Deaths, only, were considered

In contrast, McMichael et al. (82), in a retrospective cohort study of 6,678 U.S. male rubber workers followed from 1964 through 1972, found no excess in respiratory cancer mortality for the industry as a whole. In a proportional mortality study of five small plants, an excess in the proportion of lung cancer deaths among all deaths was found for three of the plants. Similarly, Andjelkovic et al. (83), using a retrospective cohort analysis, studied the 1964-73 mortality experience of a separate group of 8,418 white male rubber workers. The latter investigators reported an SMR of 80 for cancer of the respiratory system among all workers, ages 40-84, indicating an overall deficit in lung cancer deaths for the rubber workers compared to the 1968 U.S. general population. However, the investigators emphasized that use of broad age ranges in computing SMR's can mask excesses in respiratory cancer mortality found for some age groups. As an example, they cited a respiratory cancer SMR of 148 found for workers aged 40-49. Both of the preceding two cohort studies included in their separate cohorts all workers, aged 40-84, who were active or retired living employees of the rubber industry plant concerned as of January 1, 1964. Most cohort members had accrued 10 or more years of rubber industry employment prior to definitions of the cohorts.

Monson et al. (8) reported the 1940-74 mortality experience of a cohort of 13,571 white male rubber workers. They found an overall lung cancer SMR of 92, again indicating no excess lung cancer mortality for the industry as a whole.

Given data restrictions regarding the quality and availability of information, the possibility of increased risk for lung cancer associated with rubber industry employment can be explored on two levels.

First, risk for the rubber industry as a whole, considering the experience of all workers combined, regardless of their particular job experience within the industry, can be examined. This approach was used in the previously described studies, and the resulting findings were, with one exception, not indicative of an excess risk of lung cancer for all rubber workers. It has been suggested that consideration of the experience of rubber workers as a whole may lead to an inadequate assessment of risk for certain groups of workers, since exposures to hazardous materials are not uniform for all workers. Thus, an alternative approach, consisting of an evaluation of the risk associated with employment in specific work areas, must be used. Several studies, already mentioned above, have attempted to do this. Major findings, relevant to lung cancer, with special reference to specific work areas or jobs, are summarized in Table 4.

Fox et al.(4,5) found elevated SMR's for lung cancer for workers engaged in tire curing and finished goods, stores and packaging dispatch. The SMR for curing was 179 for the 1967-71 follow-up period and 111 for the 1972-74 period, while the SMR for finished goods, stores, and packaging dispatch was 193 and 129 for the first and second follow-up periods, respectively.

Mancuso (6) attempted to identify, through Social Security Administration records, all employees at a rubber products manufacturing plant in 1938 and 1939. Data was gathered on 1,568 white male workers, and their 1940-64 mortality experience was ascertained retrospectively. Mancuso found that age-adjusted respiratory cancer mortality rates for production workers in the compounding, mill, and calender department were twice the rates for Ohio males for ages 25-64 and 5.6 times the rates of Ohio males for ages 65 and above.

TABLE 4

RESPIRATORY CANCER MORTALITY IN THE U.S. & BRITISH RUBBER INDUSTRIES:
RELATIONSHIP TO SPECIFIC JOBS

Investigator(s)	Type of Study	Work Areas/Jobs of interest	Effect Measures
Mancuso, et al. (1968) (6)	Retrospective Cohort	Compounding & Milling	Rate Ratio = 2.1 (ages 25-64)
		" "	" " = 5.6 (ages 65+)
Mancuso (1974) (7)	Retrospective Cohort	Compounding & Milling	Rate Ratio = 0.57 (Company 2)
		" "	" " = 0.54 (Company 3)
		Tire & Tube Building	Rate Ratio = 1.7 (Company 3)
		" " "	Rate Ratio = 1.3 (Company 4)
		Curing	Rate Ratio = 1.8 (Company 2)
		"	Rate Ratio = 1.9 (Company 3)
		"	Rate Ratio = 5.4 (Company 4)
Fox, et al. (1974) (4)	Retrospective Cohort	Curing	SMR = 179
		Finished Goods, Stores, & Packaging Despatch	SMR = 193
Fox & Collier (1976) (5)	Retrospective Cohort	Curing	SMR = 111
		Finished Goods, Stores, & Packaging Despatch	SMR = 129

* References are noted in parentheses, following date of study publication.

TABLE 4, continued

Investigator(s)*	Type of Study	Work Areas/Jobs of interest	Effect Measures
McMichael, et al., (1976)(9)	Case-Control: N of Cases=61 N of Controls=61	Curing	Odds Ratio = 1.66 (based on exposure rate for cases=0.25 (15/61); exposure rate for controls=0.15 (9/61))
		Tire Building	no association observed
McMichael, et al., (1976)(10)	"Hybrid" N of cases=119 N of controls=1482 (based on a 22% sample of the historical cohort)	Receiving & Shipping	Risk Ratio (RR) = 1.9
		Compounding & Mixing	RR = 1.4
		Mill Mixing	RR = 2.1
		Extrusion	RR = 1.4
		Reclaim	RR = 2.3
		Tire Building	RR = 0.6
		Curing	RR = 0.8
Monson, et al., (1976)(8)	Retrospective Cohort	Curing	SMR = 160
Andjelkovich, et al., (1976)(84)	Retrospective Cohort	Synthetic Latex Manufacturing	SMR = 434

* References are noted in parentheses, following date of study publication.

McMichael et al. (10) carried out a case-control study of the association between specific rubber industry jobs and various causes of mortality. One hundred nineteen lung cancer deaths that occurred among rubber workers in a defined cohort between 1964 and 1972 were defined as cases, and a 22% sample (1,482 workers) of the original, intact cohort served as a comparison group. Rates of exposure to various work areas or jobs, directly age-adjusted to the age distribution of the sample, were computed. The exposure rates for cases and controls were compared by constructing rate ratios for each work area. A rate ratio of 1.0 signifies that there is no difference between cases and controls in exposure to a given work area.

Lung cancer rate ratios of 1.9, 1.4, 2.1, 1.4, and 2.3 were observed for Receiving and Shipping, Compounding and Mixing, Mill Mixing, Extrusion, and Reclaim, respectively.

Andjelkovich et al. (84) analyzed the relationship between work experience and mortality due to specific causes for the cohort of rubber workers mentioned above. Each worker was assigned a "most representative department"--defined as the department in which the worker spent the longest amount of employment time. A system of classification whereby rubber industry departments and work areas are grouped, according to production process similarities, into broader categories called "occupational title groups" (OTG's) was applied to the observed most representative department designations to obtain "most representative OTG's" (MROTG's). SMR's were calculated for each MROTG in order to identify work areas associated with excess lung cancer mortality. Expected numbers of deaths for each MROTG were calculated using the entire cohort as the referent group. A statistically significant excess

(SMR=434) in lung cancer deaths was observed for only one MROTG--Synthetic Latex Manufacturing. However, associations between lung cancer mortality and exposures occurring in other work areas may not have been detected in the above study, since workers' experience in work areas not designated as their MROTG's could have had an effect on lung cancer mortality patterns.

In summarization, four independent studies reporting results for lung cancer mortality among rubber workers in relation to specific jobs have given some evidence that employment in jobs involving the curing process may be associated with excess lung cancer mortality, and two studies have reported positive findings of this nature for the compounding and mixing process. Additional work areas have been implicated, but results have been inconsistent. Explanations for this inconsistency remain unclear. However, differences in study design, non-comparability across studies of work areas considered, and the possibility that observed associations are due to chance may contribute to variation in study results.

Explanations cannot presently be advanced for the apparent deficit in lung cancer mortality for the U.S. rubber industry as a whole, in contrast with the excess reported for the British rubber industry.

However, it is possible that voluntary exclusion from the U.S. rubber industry of the individuals who are more susceptible to lung cancer has occurred. This selection process and the effects it might have on findings with regard to lung cancer mortality in the rubber worker populations studied will be discussed below in general terms.

Observations from occupational mortality studies indicate that working populations have a more favorable mortality experience, in

erms of overall mortality, than the general populations to which they are frequently compared. It has been suggested that this phenomenon is the result of a selection process commonly referred to as the "healthy worker effect" (85). Such an effect may occur when one or all of the following processes acts upon the working population of interest: (1) failure of individuals having manifest disease to seek employment; (2) exclusion, according to industry pre-employment medical screening policies, of the less healthy candidate employees from the active work force; and (3) voluntary self-selection out of the work force by less healthy employees, who may have greater susceptibility to the effects of industrial exposures. Fox and Collier (86) have referred to mortality-related consequences of the first and second factors as selection effects and to those of the third factor mentioned as survival effects.

The impact of the healthy worker effect is frequently reflected in the magnitude of the all-causes SMR for the working population compared to a general referent population. An overall age-race-sex-adjusted SMR for a population of workers may be observed that is less than the SMR of 100--expected if the force of mortality for the industrial population were the same as that for the referent population--and is so often within the range of 60-80. The process of self-selection of workers out of the industry affects the calculation of SMR's only when these former employees of an industry are not included in the population-at-risk and followed for ascertainment of their mortality experience. If follow-up for all workers ever employed is achieved, the health worker effect has its greatest impact through the exclusion of candidate employees having diseases or, perhaps, risk factors for diseases that

are manifest at the time of pre-employment screening. With respect to a chronic disease whose symptoms are more likely to be detectable in older than in younger individuals, pre-employment screening will not result in effective exclusion of young workers destined to develop the chronic disease.

For lung cancer, the impact of pre-employment screening on reducing the number of individuals in the work force who are at high risk for this disease is difficult to estimate. Smoking may be considered a risk factor for several diseases. If a potential hiree has this habit or a disease whose etiology includes exposure to cigarette smoking, he may be excluded on this basis. To the extent that smoking is a strong determinant of lung cancer and smokers are excluded from the work force, the numbers of high risk workers may be reduced. This explanation for the low observed lung cancer SMR's among rubber workers is purely speculative. It is not known to what extent smokers--and especially heavy smokers--are excluded from entering the work force and, thus, to what extent the healthy worker selection effect is operative in the rubber industry.

The cohort studies of rubber workers' mortality conducted by McMichael et al. and by Andjelkovich et al. excluded from consideration most workers who were employed in the industry for fewer than 10 years. It is possible that those workers who were employed in the rubber industry for comparatively short periods of time were at higher risk for lung cancer than those who remained in the work force. The exclusion of short-term workers from enumeration in the working population-at-risk may thus have contributed to lower than expected SMR's. Fox and Collier (86) have recently studied the effects of short-term versus

long-term employment in the work force among a cohort of workers exposed to vinyl chloride monomer. They analyzed separately the mortality experience of the following two groups of workers: 1) short-term workers who left the work force before having accrued 15 years of employment; and (2) workers who had at least 15 years of cumulative experience in the industry. Sixty percent of the first group had worked for fewer than five years. Fox and Collier found that the lung cancer SMR was 156 for short-term workers, while for workers continuing to be employed, it was 50. This difference was ascribed to the retention in the active work force of healthier individuals.

D. Histologic Types of Lung Cancer

Five major histologic types of lung cancer have been described by the World Health Organization (WHO) classification system, introduced in 1967 (87):

1) Epidermoid, also called squamous, carcinoma, characterized by central or proximal site of origin and by metaplasia of columnar epithelium to form a stratified squamous epithelium with keratinization and intercellular bridges.

2) Small-cell carcinoma, including oat cell carcinoma, characterized by central location and small, round or oval cells, sparse cytoplasm, prominent nuclei, and lack of stratification.

3) Adenocarcinoma, characterized by peripheral or distal location and by formation of gland-like structures and intracellular mucin.

4) Large-cell undifferentiated carcinoma, characterized by the presence of tumor cells that are very large, are sometimes multinucleated, and have vesicular nuclei.

5. Mixed carcinomas, which usually consist of epidermoid and adenocarcinoma or oat-cell combined with other differentiated types.

TABLE 5

HISTOLOGIC TYPES OF LUNG CANCER:
ESTIMATES OF RELATIVE FREQUENCIES
OF FOUR MAJOR TYPES

Investigator(s)	References	Relative Frequency			
		Epidermoid (Squamous)	Small-cell Undifferentiated	Adenocarcinoma	Large-cell Carcinoma
Yesner, et al.	92	49.1%	19.2%	15.8%	15.5%
Shinton	89	57.2%	30.2%	4.0%	-
Berg	94	47.0%	17.0%	10.0%	17.0%
Weiss, et al.	96	61.3%	12.9%	22.6%	6.5%

* Oat-cell carcinomas, only.

will be more frequent in autopsy series. Thus, in series not based on complete ascertainment of lung cancer cases in a defined population, the distribution of histologic types will be subject to selection bias.

The problem of selection bias may be alleviated by use of a cohort study design. Weiss, et al.(96) in a prospective study of 6,136 men at least 45 years of age at the beginning of the study, detected 121 cases of lung cancer during the 10-year follow-up period. Subsequent analysis was confined to 2,580 men who were current smokers at the initiation of the study, since lung cancers developed only among this subset of the original study population. The following distribution of histologic types based on material available for 67 of the cases, was reported: epidermoid, 61.3%; small-cell, 12.9%; adenocarcinoma, 22.6%; and large-cell, 6.5%. Although this study design would, in theory, diminish the possibility of selection bias, histologic diagnosis was unavailable for almost half the cases. Therefore, because of incomplete ascertainment of histologic types, it cannot be assumed that the observed pattern was an accurate reflection of the true distribution of histologic types.

Shinton (89) pointed out that each histologic type of lung cancer has characteristic biological features and cited differences among the various types in age and sex distribution, location in the respiratory system, occurrence of metastases, and survival prognosis. He concluded that lung cancer is a heterogeneous disease and that each of the histologic types may be associated with a distinct etiology. Cigarette smoke was the first etiologic agent to be examined in terms of its influence on the distribution of histologic types of lung cancer.

Kreyberg (88) studied a series of 522 male and 78 female lung cancer cases collected in Norway. He suggested that epidermoid and small-cell carcinomas are associated with cigarette smoking, while the development of adenocarcinoma is not influenced by cigarette smoke. He calculated proportional mortality ratios (PMRs) for the various types for smokers compared to non-smokers. Comparisons of the PMRs over categories of amount smoked demonstrated that PMRs for epidermoid and small-cell carcinomas increased for each 5-gram increment in amount smoked per day, while PMRs for adenocarcinoma remained constant over all smoking strata. In addition, Kreyberg noted that adenocarcinoma accounted for 45% of the 78 female cases but only 13% of the male cases. He postulated that this observed difference was a product of lower prevalence of smoking among females and consequent elevated frequency among females compared to males of adenocarcinomas, possibly developing in response to etiologic factors other than cigarette smoke.

Yesner et al.(93) examined histologic type and smoking habits of 449 lung cancer cases derived from a biopsy series collected between 1953 and 1959. Adenocarcinoma, with a frequency percent of 57.1%, was the predominant type among non-smoking cases, while among cases who smoked, epidermoid carcinomas predominated. Auerbach et al.(97) examined an autopsy series that included six non-smoking cases, all of whom were diagnosed as adenocarcinoma. Age-adjusted percentage distributions of the histologic types found among smokers were examined by cigarette smoking categories. The percentage of adenocarcinomas decreased from 29.2% among those smoking less than one pack per day to 20.1% among those smoking two or more packs per day. In contrast, the percentage of small-cell carcinomas increased from 19.2% for those smoking

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less than one pack per day to 31.1% for those smoking 2+ packs per day. No differences according to amount smoked were noted for epidermoid or large-cell carcinomas over the same range of cigarette consumption.

In contrast to the above studies, which suggest an association between smoking and distribution of histologic type of lung cancer, the study of Weiss et al. (96) does not indicate that such a relationship exists. The latter investigators compared age- and race-adjusted rates of mortality due to the five major types of lung cancer among categories of smoking and found that epidermoid, small-cell, and adenocarcinomas all showed a dose-response relationship with amount of cigarette smoking.

There is evidence to suggest that environmental carcinogens other than cigarette smoke may also influence the distribution of histologic types of lung cancer in exposed populations. Whitwell et al. (98) studied the histologic types of lung cancer found among workers with certified asbestosis who died in the United Kingdom between 1962 and 1972. There were 88 male cases available for study, or 67% of all lung cancer cases having concomitant asbestosis. Adenocarcinoma was found to be the predominant type of lung cancer for all grades of asbestosis, and the distribution of cigarette consumption did not vary among the histologic types. The authors of this study concluded that their identification of adenocarcinoma as the predominant type of lung cancer among workers with asbestosis was unusual. They suggested that asbestos dust can reach the distal areas of the bronchial tree and, acting as a cocarcinogen with cigarette smoke, can give rise to adenocarcinomas.

Saccomanno et al. (99) studied 121 cases of lung cancer that occurred between 1949 and 1969 among Uranium miners, in order to evaluate the association between radon daughter exposure and distribution

of histologic types of lung cancer. One hundred thirty-eight lung cancer cases in non-miners, occurring in the same geographical area during the same time period, constituted a referent group and were matched with miners on age and cigarette smoking habits. Distributions of histologic types among miners and the referent group were compared. At every level of radon daughter exposure, the proportion of small-cell carcinomas was higher for Uranium miners than for the referent group. The authors concluded that radiation exposure influences the distribution of histologic type of lung cancer among Uranium miners and that, while cigarette smoke is a potent co-carcinogen, it exerts little influence on histologic type of lung cancer in the population of miners studied.

Figueroa et al. (72) as mentioned previously, reported the 1962-1967 lung cancer mortality experience of 125 men with industrial exposure to chloromethyl methyl ether (CMME) and it contaminant BCME. Four cases of lung cancer occurred. Ten additional cases were detected among employees exposed to CMME and BCME prior to 1962. Histologic type was determined for 13 of these cases, and 12 were classified as small-cell carcinomas. Although the series of cases is small and ascertainment of cases for workers exposed prior to 1962 may be incomplete, these findings suggest that the distribution of histologic type of lung cancer is influenced by exposure to CMME or BCME.

Waxweiler et al. (74) in the retrospective cohort study of vinyl chloride workers described previously, were able to examine histologic material for eight of the 12 lung cancers that were detected. Five cases were classified as large-cell undifferentiated carcinoma and three as adenocarcinoma. The predominance of large-cell carcinomas

and adenocarcinomas and the absence of epidermoid and small-cell carcinomas is unusual.

Findings of the above-mentioned studies suggest that specificity of histologic type of lung cancer may be determined, in part, by etiologically relevant environmental exposures and that different carcinogens may contribute to the observed variability in patterns of distribution of the histologic types. Radon daughter and CMME (or BCME) exposures result in an elevated relative frequency of small-cell carcinomas; asbestos exposure, in adenocarcinoma; and vinyl chloride, in large-cell and adenocarcinomas. Study of the distribution of histologic types of lung cancer occurring among populations whose specific exposure is unknown may provide clues to or indicate the presence of unusual carcinogens in their environments.

E. Summary of the Background Information and Literature Review

1. Lung cancer mortality exerts a considerable impact on the health of the general population and on the labor force, in terms of work-years lost. The 1940-67 increase in rates of lung cancer mortality in the U.S. has occurred for all race-sex groups and has been most dramatic for white males, ages 35-44, for black males, and, since 1960, for females.

2. Lung cancer mortality rates show considerable geographical variation, both within the United States and on a world-wide level. Environmental and host-susceptibility factors may, in combination, influence the observed variability. Known risk factors for lung cancer include the following: age, sex, race or ethnicity, urban residence, migration, smoking, and occupation.

3. Although trends in lung cancer mortality largely reflect cigarette consumption patterns, agents encountered in occupational settings may have an impact on lung carcinogenesis. A probable causal association between occupational exposures and lung carcinogenesis has been demonstrated for radon daughter, asbestos, arsenicals, and coal carbonization products exposures and has been suggested for a number of additional industrial exposures.

4. Studies of the rubber industry have shown lung cancer mortality to be elevated for certain work areas. However, these studies have not consistently indicated that elevated lung cancer mortality is specific for a particular work area. Therefore, it has not been possible to identify agents having etiologic significance.

5. There is evidence to suggest that occupational exposures, such as radon daughter, BCME, and vinyl chloride, may cause the relative frequencies of the histologic types of lung cancer to fluctuate from the distribution found among a general population, whose usual exposure is cigarette smoke. Therefore, inspection of the distribution of histologic types of lung cancer found in an industrial population may provide insight into the nature of the exposures responsible for lung cancer induction and may aid in distinguishing lung cancers arising in response to cigarette consumption from those developing as a result of occupational exposure.

(2) As indicated in the accompanying literature review, certain groups of migrants, both foreign-born and those migrating within the U.S., have excessive lung cancer mortality, compared to native Ohio residents. However, studies of the relationship between migrant status and lung cancer mortality have not investigated the possibility that migrant status exerts its influence through the differential employment of migrant workers in hazardous occupations. Therefore, the second objective of this study was to evaluate the residual effect, if any, of migrant status on lung cancer mortality among a relatively homogeneous population of rubber workers at an Ohio rubber plant.

With respect to the first objective stated - that is, to determine which work areas, if any, are associated with an increased risk of lung cancer mortality - it was expected that the following relationships would be present for any work area found to be associated with increased lung cancer risk:

(1) mean duration of employment in that work area would be greater for workers who died of lung cancer than for those who remained free of the disease until their death;

(2) relative risk of lung cancer for workers having a history of employment ("exposed") in a given work area, compared to workers who never worked ("unexposed") in the work area, would increase with increments in a minimum duration of exposure criterion demonstrating consistency with the dose-response concept, where "dose" is defined as duration of exposure to a specific work area and "response" is indicated by lung cancer risk; and

insure that cases and their respective controls had equal opportunity for exposure. The process of selection of cases and controls and the definition of exposure variables will be discussed in greater detail later. Rationale for selecting the case-control mode of investigation is presented below.

A. Rationale Underlying the Choice of Study Design

Choice of a case-control study design was based on the consideration of two issues. The first of these concerned the appropriateness of the design for fulfilling the primary research objective, which was to identify workers who may be at increased risk for lung cancer by virtue of their employment in specific rubber industry jobs, and the second concerned the feasibility of implementing the chosen design.

In case-control studies, disease incidence rates and cumulative incidence rates are not known. Therefore, direct quantification of disease rate ratios and risk ratios (relative risks) for exposed subjects compared to unexposed subjects cannot be carried out. Information regarding the probability of disease given exposure can be directly obtained only from retrospective or prospective follow-up (cohort) studies. However, relative risk may be approximated in case-control studies by the odds ratio (100, 101). This parameter is estimated by dividing the ratio of exposed to unexposed cases by the ratio of exposed to unexposed controls. Thus, the odds ratio is the ratio of the exposure odds for cases compared to non-cases. It has been shown that, when the probability of disease in the source population is low (less than 20%), the difference between estimates of the risk ratio (relative risk) and the odds ratio is trivial (100, 101). Furthermore, Miettinen (102) has

shown that, when incident cases are considered, and controls are drawn from a defined population, odds ratios derived from case-control studies estimate incidence density ratios and, thus, instantaneous risk ratios, without the assumption that the disease of interest be rare. The case-control method, therefore, provides a means for estimating an appropriate effect measure - the odds ratio - which is useful for evaluating possible associations between a disease and exposure of interest and for assessing the magnitude of any association found.

Prospective and retrospective follow-up studies, in which exposures are measured at one point in time and subsequent disease occurrence among exposed and unexposed subjects is ascertained during or after a specified interval of time, constitute alternative modes of investigation that offer the following advantages over case-control studies (101): (1) direct quantification of rate ratios or relative risks is possible, since either incidence or cumulative incidence rates may be calculated; (2) if attrition does not occur and if disease rates are ascertained for all members of the study population, selection bias will not be introduced; and (3) when the distorting effects of potential confounders are controlled and when selection bias and misclassification errors are not present, follow-up studies provide more convincing evidence than case-control studies for the presence of causal relationships, since the follow-up method distinguishes disease that occurs as the result of exposure from that which occurs concurrently with exposure or prior to exposure. The problem of determining whether an observed association between disease and exposure is causal when a case-control study, in which exposure is measured retrospectively, is used can be partially overcome by careful exclusion from consideration of exposures that may be irrelevant because

of insufficient lapsed amount of time between the onset of exposure and disease occurrence. An additional advantage of the prospective follow-up method is the possibility for investigator control over the types and accuracy of measurements of both the exposure variable(s) and potential confounders of interest. Retrospective follow-up and case-control studies often suffer from absence of useful data or inadequacy of certain aspects of available data.

Major obstacles confronting the application of prospective and retrospective follow-up study designs derive from the issues of convenience and economy. Consideration of these issues was the second factor leading to the choice of the case-control study method. The prospective approach was not feasible for studying the association between rubber workers' lung cancer mortality and job exposures, since the lung cancer latent period associated with occupational exposures often exceeds 15-20 years. Therefore, the minimum follow-up period that must be allowed for the detection of any effect of exposure on risk of lung cancer precludes the use of a prospective design. In addition, since lung cancer is a comparatively rare disease, a prohibitively long amount of time or large population must be provided in order to compile a case series of appropriate size for estimating effect measures and drawing inferences with respect to these measures. Finally, subjects included in a prospective study must be classified according to exposure at the outset of the study, and this design is therefore not feasible for the investigation of multiple exposures.

or a representative sample thereof, for whom ascertainment was not determined by exposure status, are considered; (2) the controls included in the study population have exposure rates that are equivalent to those experienced by non-diseased individuals in the source population; and (3) no misclassification with respect to disease status has occurred.

Violations of these assumptions may lead to systematic error or bias in estimation of relative risk and thus contribute to the major limitations of case-control studies. With regard to the first assumption, failure to enumerate all cases because of attrition from the source population prior to identification of the case series to be studied may result in the selective inclusion in the study of cases having non-representative exposure histories. With regard to the second assumption, if the cases considered in the study are representative but the exposure rate among study controls is lower than the true exposure rate among non-diseased individuals in the source population, the effect measure (odds ratio) will be exaggerated. Conversely, if the exposure rate for the study controls is higher than the true rate among non-diseased members of the source population, the effect measure will be underestimated. Representativeness of cases and controls selected for this study will be discussed later. With regard to the third assumption, an attempt was made to ascertain all rubber worker lung cancer deaths occurring during a specified period of time (83). However, it is, in fact, not possible to estimate the number of undetected deaths due to lung cancer, and some of these may have been included in the control series. Also, some of the subjects included in the case series may have been erroneously diagnosed as having lung cancer.

C. Design Considerations

1. Description of the Source and Sample Populations

Although it may be desirable to consider the theoretical source population for the current study as all workers ever employed at the rubber plant of interest, in fact, the lung cancer cases and referents comprising the study population were members of a cohort of rubber workers identified at a single rubber manufacturing plant in Ohio. This cohort has been described previously (83). Construction and follow-up of the cohort are reviewed below, and methods used to select cases and controls are discussed.

The fixed cohort, henceforth referred to as the "1964 Cohort" consisted of all active or living retired hourly workers at the plant of interest who were at least 40 years old as of January 1, 1964. The 1964 Cohort was identified through examination of available company personnel and union records. The mortality experience of the entire cohort of 8,938 workers and the subset of 8,418 white male members was ascertained for the ten-year period, ending on December 31, 1973, and is summarized in Figure 1.

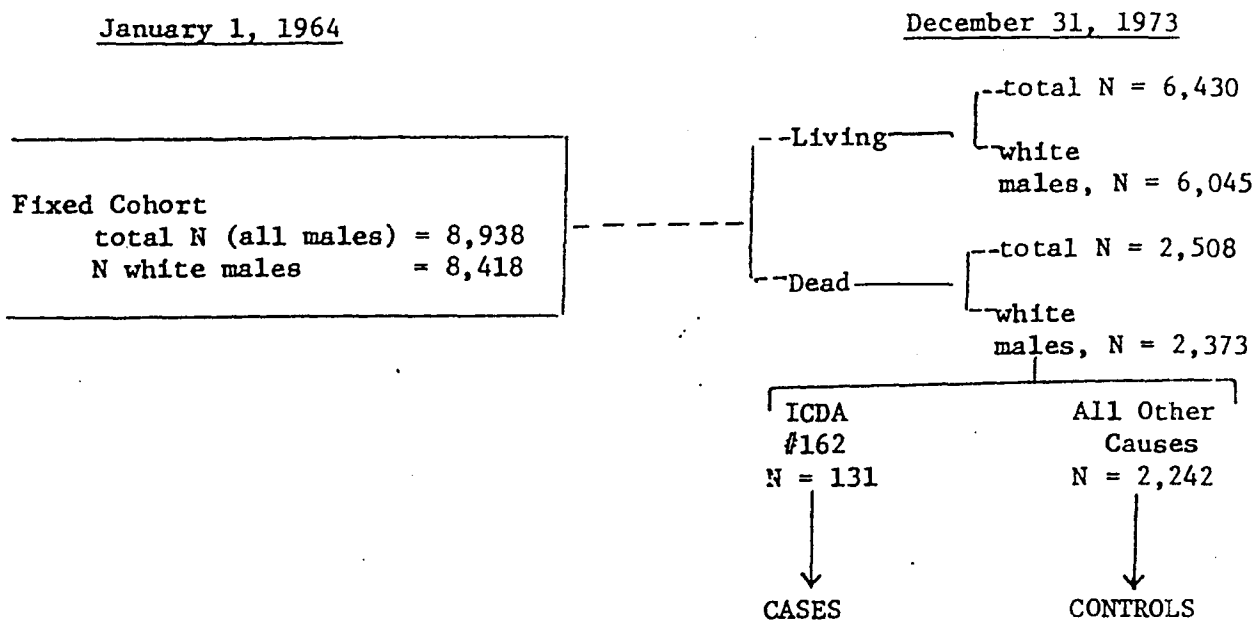

Figure 1: Mortality experience of the 1964 Cohort of rubber workers.

The vital status of Cohort members was determined through company insurance benefits records and the Bureaus of Vital Statistics of various states. Follow-up was 96.7% complete. Information pertaining to cause of death was obtained from death certificates available for approximately 98% of Cohort member deaths.

The 1964 Cohort excludes the following groups of workers who may be considered as members of the conceptual source population: (1) workers who were listed as members of the 1964 Cohort but who could not be traced; (2) former employees who died before 1964; (3) employees who were living but were under 40 years of age on January 1, 1964; and (4)

former, short-term, employees who quit the industry before qualifying to receive retirement benefits. As indicated above, the number of workers who could not be traced is small, and it is therefore unlikely that differences in disease rates or exposure patterns between these individuals and the successfully followed portion of the 1964 Cohort could affect the results of the current study. Of major concern to the validity of making inferences from results based on members of the 1964 Cohort are the second, third, and fourth groups enumerated above. For the purpose of drawing inferences with respect to all employees of the plant from the results of this study, it must be assumed that exposure "rates" for these individuals were comparable to those experienced by workers included in the 1964 Cohort. The correctness of this assumption is not known.

All deaths occurring among 1964 Cohort members during the 10-year period of 1964 through 1973 constituted the source for both cases and controls. White males only were included in the current study, since black male and female workers would have to have been considered separately for reasons of validity, and numbers of lung cancer deaths among the latter two groups were small. White males comprised approximately 94% of the 1964 Cohort of rubber workers.

As shown in Figure 1, 131 white male hourly workers died with a diagnosis of primary lung cancer (ICD #162) at some level of causation on their death certificates, These were designated as cases. The 2,242 white male deaths due to all causes other than malignant neoplasms of the respiratory system constituted the comparison group from which the controls included in this study were selected. Five-hundred controls were individually matched with cases on year of birth and year of first hire at the plant under study. One to 4 controls were chosen for each

case, depending on availability within the matching restrictions. A detailed discussion of the selection of controls for the present study will be presented in the following two sections.

2. Validity with Respect to Selection of Cases and Controls

A desirable property of any epidemiologic study design stipulates that, under the null situation of no association between the exposure(s) and health outcome of interest, study subjects should be chosen so that exposure "rates" are the same for cases and controls (in case-control studies) or so that disease incidence rates are equal among exposed and unexposed subjects (in follow-up studies). For case-control studies in which the case group consists of all cases or a representative sample of all cases, it is desirable for the referent group also to be representative, in terms of exposure, of all non-diseased members of the source population. Two issues relevant to the attainment of this property in the present study warrant discussion.

First, it was necessary to limit the pool of eligible controls to all deaths, other than those due to cancer of the lung, rather than to select controls from among all members of the 1964 Cohort, regardless of vital status at the termination of the follow-up period, because complete work history information was available for deceased workers only. Thus, for any work exposure that is positively associated both with lung cancer mortality and with death due to another cause or with vital status in general, differences between cases and controls with respect to the exposure will be underestimated. In effect, then, one possible result of this aspect of the study design will be to dilute estimates of relative risk. This limitation is inherent in the design of the study

and cancer of another site, the ability to detect differences between cases and controls in this factor will be reduced. The inclusion in the comparison group of deaths from other cancer causes also associated with the factor in question would result in spuriously elevated exposure "rates" among the controls, and, again, effect measures estimated would be biased towards the null. In order to ascertain the extent of the possible bias introduced by including deaths due to other malignant neoplasms in the control group, the distribution of deaths due to cancer among the controls may be examined, and analyses based on the total control group (other cancer deaths and non-cancer deaths, combined) and on the subset of controls comprised of non-cancer deaths only may be compared. These latter analyses have not yet been completed.

3. Validity with Respect to Control of Potentially Confounding Variables

Because of the alterations in production processes in the rubber industry, jobs and associated exposures may have changed qualitatively and quantitatively over time. For example, workers who entered the industry in 1930 may have had the opportunity for contact with materials that were not used in the 1940's. Thus, workers who initiated their employment in the industry at different points in time may not have had equivalent opportunity for employment in the same types of jobs or may have encountered qualitatively different exposures in the same jobs because of changes occurring over time in materials used. For this reason, it was necessary to control for year of first employment. It was decided to carry out individual matching of cases with controls on year of first employment at the plant under study ($\pm$ 1 year), since

stratification in ensuing analyses as an alternative control procedure would be inefficient and might lead to loss of internal validity due to differences between cases and controls in year of first hire within strata of this variable. In addition to year of first hire, race, sex, and age were thought to be potential confounders of the association between lung cancer mortality and work history patterns. These variables were considered at the design stage of the study by one of the following methods: (1) subject category restriction or (2) matching.

In order to be a confounder, a factor must both be associated with the exposure of interest and be a predictor or risk factor for the disease, independent of exposure. Race and sex are known predictors of lung cancer mortality. In addition, it is possible that both a worker's race and sex may have influenced his/her choice of or assignment to jobs within the rubber industry. Age may be a confounder by virtue of its known positive association with lung cancer (i.e., lung cancer death rates increase with age) and its possible association with work history. An association between work history and age may have arisen in the study population if some factor, such as company employment practices, led to the differential assignment of workers to particular jobs depending on age.

The potentially confounding effects of race and sex were controlled for in the current study by restricting eligibility for inclusion in the study to white males. The effects of age were considered in the study design by matching cases and controls on year of birth ($\pm$ 3 years), and by requiring that controls must have lived at least as long as their respective cases. By stipulating that the controls must have achieved the same or a greater attained age at death as their respective cases,

it was intended to accomplish the following: (1) the possibility of systematically excluding controls who may have lived longer than respective cases because of differences in exposures will be reduced, and the ability to detect differences between cases and controls in exposures having health effects of interest will be enhanced; (2) the possibility of including as a control an individual whose exposure may have been etiologically relevant to lung cancer but who died of another cause before lung cancer became manifest will be minimized; and (3) comparisons of "old" cases with "young" controls will be avoided, and the variability of unmeasured or unknown lung cancer risk factors that are correlates of age will be controlled.

The matching scheme employed in the current study - i.e., matching on both year of birth and year of first hire in the rubber industry - in addition effectively limits case-control differences in age at first hire. For example, it would be undesirable to compare a case who was first hired at age 20 with a control who was 40 years of age when he initially entered the rubber industry. These individuals may differ with respect to unrecognized or unmeasured lung cancer risk factors that are correlates of age at first hire, and age at first hire may be a determinant of subsequent work history pattern: for example, older workers may be placed in less demanding jobs involving less severe exposures and may have less opportunity for job mobility, compared to younger workers.

An additional potential confounder that could not be considered because pertinent data were unavailable was cigarette consumption by study subjects. As noted previously, cigarette smoking is the strongest

known risk factor for lung cancer. If cigarette consumption were distributed unequally among the different groups of workers, categorized by their work history, who are compared in the present study, it cannot be known whether associations observed are attributable to materials encountered in the work environment or to cigarette smoking. Although it was not possible to consider the cigarette smoking habits of cases and controls, it was thought that, by matching on year of birth, cases and respective controls would at least belong to the same birth cohort of smokers. This is important since cigarette smoking habits, in general, vary according to birth cohort membership.

As explained above, individual matching on year of birth and year of first hire was conducted, with the additional constraint that controls must have lived at least as long as their respective case. Controls' year of birth was allowed to vary by plus or minus three years from their respective cases' year of birth, and year of first hire was allowed to vary by plus or minus one year. It was felt that differences between cases' and controls' values of these variables resulting from permitting the above ranges would be inconsequential. Furthermore, this procedure permitted the selection of more controls per case. Four controls per case were sought in order to increase the sample size used in the study and, thus, the precision of parameter estimation. However, the matching ratio was allowed to vary from 4:1 to 1:1 when fewer than four controls were available for a case.

D. Sources and Adequacy of Data

In order to obtain unbiased risk estimates, information with respect to the exposures of interest, disease status, and other (control) factors should be of the same quality for cases and controls. The source of data for constructing the case series and the pool of eligible controls consisted of death certificates for all deaths occurring among members of the 1964 Cohort during the ten-year follow-up period. All death certificates were nosologized according to the Eighth Revision of the International Classification of Diseases (ICD). Death certificates were not available for four (< 1%) of the study subjects. For these individuals, cause of death was determined by examination of company insurance benefits records. As previously noted, it is not known to what extent study subjects were misclassified according to their lung cancer status. Although it is possible that some of the controls selected had an undetected lung malignancy, there is no reason to believe that failure to detect lung cancer is associated with exposure (work) history. Hence, any errors due to misclassification by disease status are likely to be non-differential and will lead to conservative estimates of effect. Additional information obtained from death certificates included dates of birth and death and place of birth (state or country, if foreign-born).

Detailed job information for each study subject was obtained from company employment records. These records will be referred to as work histories. It has been assumed that the work histories are essentially complete in terms of listing all jobs held and that the completeness and accuracy of the work histories are not dependent on case-control status,

so that any misclassification with respect to exposure was non-differential. Again, there is no reason to suspect that differential classification errors have taken place.

As previously noted, "exposure" in the current study is defined as occurrence and duration of employment in certain rubber industry production work areas. There are numerous jobs in the rubber industry, each involving diverse qualitative and quantitative exposures to chemically complex work environments, and an individual worker may move through more than 30 jobs during the course of his employment at a rubber plant (103). The chemicals that were used in or generated by a given production process can seldom be identified, and quantitative information is not available. For most jobs, both the exact chemical composition and the amount of materials constituting the major exposures are unknown. Thus, because of the chemical complexity of the work environments encountered by rubber industry employees and the currently incomplete characterization of these environments, it is not feasible in most instances to objectively classify workers according to categories of exposure to specific chemical agents and subsequently to determine disease risk associated with these exposure categories. An alternative job classification scheme - the Occupational Title Classification System - has been devised (103). This classification system groups together jobs on the basis of similarities in materials used, production process involved, and/or products produced. Thus, jobs that involve relatively homogeneous conditions with respect to type of raw materials or products encountered may be grouped into units called "Occupational Titles (OT's)". The resulting OT's may then be aggregated - again on the basis of products or processes involved - into a smaller number of "Occupational Title Groups (OTG's)". For the

present study, 119 OT's grouped into 21 OTG's were considered. OTG's 1-20 involve active employment, while OTG 21 is reserved for absence periods and exits from the industry and will not be considered in the analyses. Lists of the OT's and of the OTG's and their component OT's are given in Appendix A-1 and A-2. Although a complete characterization of the OTG's is not possible, industrial hygienists have been able to ascertain the major environmental hazards encountered in each OTG. This description is included in Appendix A-3.

As noted previously, the present study was directed toward assessing the relationship between lung cancer mortality and employment experience in two work areas - Compounding and Mixing (OTG 1) and Curing (OTG 9) - found in previous studies to be associated with increased lung cancer risk, and toward detecting possible associations with other work areas. s defined in the present study, the Compounding and Mixing work area is comprised of 12 OT's, and the Curing work area contains 7 OT's. In addition to the potential exposures mentioned in Appendix A-3, a list of specific chemicals which are reported to have been present in these OTG's, although not necessarily in this plant, and known to constitute respiratory system hazards is given in Table 6. Some of these compounds, such as lead chromate, are or have been used in relatively small amounts.

The decision to use OTG classifications rather than some other method of grouping jobs according to exposure was made for the following reasons: (1) there were no clear-cut, a priori hypotheses regarding a specific subset of jobs clearly different from the job groups composing the OTG's; (2) the OTG classification results in job groupings similar to those previously investigated by other researchers and thus facilitates

Table 6

Known Chemical Respiratory System Hazards Reported to Have Been Used in the Rubber Industry in the Compounding and Mixing and the Curing OTG's*

OTG	Chemical Compound	Use in the Rubber Industry	Comments
pounding & xing	Cadmium compounds[1]	-accelerator	-Cd. is a possible carcinogen
	Chromates[2]	-present in pigments	-lung irritant & carcinogen
	Carbon Black	-filler	-lung irritant
	Zinc oxide	-accelerator; activator	-lung irritant
	Talc	-filler; coating of green rubber	-lung irritant; may be contaminated with asbestos, a lung carcinogen
	Phenols (phenol-form-aldehyde resins)	-bonding agents	-lung irritant; tumor promoter; ciliostatic agent
ng	Talc	-see above	-see above
	Phenols	- "	- "

es: OHSG: unpublished environmental data.
References 49-53, 56, 63-67, and 36.
suspected roles as respiratory system hazards of most of these compounds have been ussed in greater detail in the Literature Review section of this paper.

ium diethyldithiocarbamate is the specific accelerator used. The carcinogenicity his Cadmium compound is unknown.

chromate salts have been used as pigments. The carcinogenicity of the specific ounds used at the plant under study is unknown.

comparison of the current study's results with earlier reports in the literature; and (3) the use of the relatively small number of OTG's to summarize job information was necessary in order to obtain adequate numbers of subjects having employment experience in the work areas of interest for derivation of statistically stable risk estimates.

The detailed work histories obtained from company records for each subject consisted of the worker's name and social security number and the following information for each consecutive job change: the complete date in and date out for the job, a description of the job, and a department code for the job. These work history records were summarized as follows: (1) the date of first employment in the rubber industry and the date on which the worker terminated the last job he held at the plant were noted; (2) the amount of time spent in each job was computed; (3) each job was assigned an OT and an OTG by a computerized job-OT-OTG dictionary; (4) the amount of time spent in each OT and in each OTG was calculated by accumulating total time spent in the jobs constituting the appropriate OT's and OTG's (if the cumulative amount of time spent in an OT was less than 15 days, the duration of employment in this OT was counted as zero); (5) the year of first employment in each OT and each OTG was computed as the earliest year in which the worker was employed in any job belonging to the given OT or OTG; (6) the total amount of time spent as an active worker in the rubber plant was calculated by summing over the time spent in each OT involving active employment.

Exclusions of 62 initially selected subjects occurred for the following reasons (also, see Table 8):

(1) if, for either cases or controls, no work history could be located;

(2) if, for either cases or controls, the work history was found to be incomplete;

(3) if, for controls only, the respective case was excluded because of missing or inadequate work history information;

(4) if, for cases only, no suitable match was found.

E. Analyses

In order to assess the results and adequacy of the matching procedure, differences between each case and the average among his corresponding controls for year of first hire, year of birth, and age at first hire were computed. The mean of the differences ($\bar{D}$) was computed for each of these variables and the null hypothesis, H_o: $\bar{D} = 0$, was evaluated, using the paired sample t-test (see Appendix B for formulae). Also, the group means of these variables for cases and controls, ignoring the matching, were calculated for descriptive purposes.

The means for cases and controls for age at death and the mean difference between each case's age at death the average age at death among his respective controls were also evaluated in order to determine whether controls lived longer than cases and whether cases' age at death was lower than might be anticipated, since early death from lung cancer may be indicative of heavy or unusual, and possibly work-related, exposures.

The frequency distribution of length of overall employment and the mean duration of overall employment were determined separately for cases and controls and were compared, using the chi-square test and the two sample t-test (see Appendix B). Also, the paired sample t-test, which

takes matching into account, was calculated for the mean difference between cases and respective controls in length of overall employment.

The question of equivalency of total duration of overall employment between cases and controls is of importance in evaluating the association between OTG-specific employment and lung cancer risk. It is desirable for cases and controls to have had equal opportunity for employment in the OTG of interest. It is reasonable to expect that, as a subject's cumulative length of employment increased, his opportunity to move into a given OTG also increased. Thus, for example, if a case had been employed for a longer period of time than his control, the case may have had a greater chance to have worked in any given OTG. If this occurred, relative risk estimates would be biased upwards. Such a bias is avoided if cases and controls are not different with respect to cumulative duration of employment or if controls having shorter duration than cases are excluded. A bias in the opposite direction may occur if cases worked for a shorter period of time than controls, and this bias may be overcome by restricting consideration of controls' work histories to the period defined by respective cases' cumulative duration of overall employment. Preliminary analyses were based on the complete work histories of all cases and controls included in the study.

Migrant status for study subjects was ascertained from place of birth information recorded on death certificates. A migrant in the present study was defined as any subject not born in the State of Ohio. In order to compare the results of the present study with those of Mancuso (40,41) and others, migrants were further classified into one of the following groups: (1) European or foreign-born migrants, (2) migrants

from the southern U.S.A., including the states of Kentucky, Tennessee, Georgia, Alabama, Louisiana, Arkansas, Mississippi, Virginia, North Carolina, South Carolina, Florida, Maryland, Texas, and Oklahoma; (3) migrants from the northeastern U.S.A., including the states of Pennsylvania, New Jersey, New York, and Connecticut; and (4) migrants from central U.S.A., including the states of West Virginia, Indiana, Illinois, Nebraska, Michigan, and Kansas. Other states and geographical regions of the U.S.A. were excluded from the above classifications since no subject was born in these areas. Percentages of native Ohioans and of each migrant group were determined for cases and controls, and the statistical significance of observed differences was tested, again using the chi-square test.

Next, OTG-specific employment was considered. Several analyses, based on subjects who fulfilled some minimum duration of OTG-specific employment criterion, were carried out. The percentages of cases and controls employed in each OTG were ascertained separately for three minimum duration of employment categories: (1) ever (more than 15 days) employed in the OTG of interest; (2) employed for at least 2 years in the OTG of interest; and (3) employed for 5 or more years. The second and third categories mentioned above are not mutually exclusive, and both represent subsets of the first duration of employment category. Statistical significance of differences between proportions of cases and controls falling into each category were tested separately for each OTG by the chi-square test. For this test, the proportion "exposed" (employed) is defined by the number of subjects meeting the minimum duration criterion in the OTG specified, divided by all other subjects having the same disease status. For example, the proportion of cases "exposed" to OTG 1 for 5 or more years is given by the number of cases whose cumulative

employment in OTG 1 was 5 or more years in duration, divided by the number of cases who spent fewer than 5 years in OTG 1 or were never employed in OTG 1.

It was then desired to quantify the risk for lung cancer associated with employment in each of the 20 "active" OTG's. As previously discussed, the appropriate measure of effect, in terms of risk, for case-control data is the odds ratio ($\widehat{OR}$). Data layout for calculation of a crude odds ratio is illustrated in Figure 2.

	Case-Control Status		
	Cases	Controls	Total
Exposed	a	c	m_1
Not Exposed	b	d	m_0
	n_1	n_0	N

Where, a,b,c, and d represent the number of subjects falling into each exposure-case/control-specific classification; n_1=total number of cases; n_0=total number of controls; m_1=total number of exposed subjects; m_0=total number of unexposed subjects; and N=total number of all study subjects.

Figure 2. Data layout for calculation of the crude odds ratio ($\widehat{OR}$) in case-control studies.

Source: Reference 100.

The point estimate of the odds ratio is given by

$$\widehat{OR} = \frac{ad}{bc}, \qquad (1)$$

and the appropriate test of the statistical significance of the association represented by the $\widehat{OR}$ is the chi-square test with 1 degree of freedom (104). Formulae used for computing this test statistic and for deriving

test-based confidence intervals are given in Appendix B. The null hypothesis of interest is given by H_0: $\widehat{OR} = 1$.

It has been shown (105) that the crude $\widehat{OR}$ is an unbiased estimator only when the proportion of exposed who are positive for the matching variable is equal to the proportion of non-exposed subjects who are positive for the matching variable, where the matching and exposure variables are both dichotomous. This statement is applicable, also, to the current study, in which matching variables are continuous, and it implies that the crude $\widehat{OR}$ will be unbiased only when there is no association between the exposure agent and the matching variate. When any such association exists, the crude OR will be biased, even when the covariate is not a confounder: i.e., even when the covariate is not associated with the disease (as is expected, as a result of the matching procedure).

In case-control studies with individual matching, unbiased estimates of relative risk can be obtained only by performing stratified analyses (assuming that exposure is associated with the matching variates), where each stratum consists of a case and his respective controls. As mentioned previously, depletion of the pool of eligible controls in the current study resulted in there being a variable matching ratio (R). However, matched quintuplets (R=4:1) were obtained, when possible. Thus, the method used for computation of the unbiased $\widehat{OR}$ for matched quintuples will be demonstrated; then calculation of the $\widehat{OR}$ when a variable matching ratio is used will be presented.

Data layout for calculation of the $\widehat{OR}$ given a 4:1 matching ratio is shown in Figure 3. Referring to this figure, the $\widehat{OR}$, as derived by Mantel and Haenszel (104), is defined by the following equation:

$$\widehat{OR} = (4f_{10}+3f_{11}+2f_{12}+f_{13})/5 \quad / \quad (4f_{04}+3f_{03}+2f_{02}+f_{01})/5 \qquad (2)$$

		Number of Controls Positive for Exposure					
	Cases	4	3	2	1	0	
	Exposed	f_{14}	f_{13}	f_{12}	f_{11}	f_{10}	$f_{1\cdot}$
Not	Exposed	f_{04}	f_{03}	f_{02}	f_{01}	f_{00}	$f_{0\cdot}$
		$f_{\cdot 4}$	$f_{\cdot 3}$	$f_{\cdot 2}$	$f_{\cdot 1}$	$f_{\cdot 0}$	$f_{\cdot\cdot}$

Where the f_{ij} = the number of matched groups having i cases and j controls with the exposure response indicated.

Figure 3. Layout and notation for data from case-control studies with 4:1 matching and dichotomous outcome and exposure.

Sources: References 104 and 106.

In the variable matching ratio situation, where the ratio may vary from 1:1 to 4:1, four subseries of matched groups, each having a fixed number of referents per case, must be considered: i.e., pairs, triplets, quadruplets, and quintuplets. For pairs, an odds ratio is obtained as follows:

$$\widehat{OR} = (f_{10})/2 \quad / \quad (f_{01})/2 \qquad (3)$$

For triplets, the analogous odds ratio formula is:

$$\widehat{OR} = (2f_{10}+f_{11})/3 \quad / \quad (2f_{02}+f_{01})/3 \qquad (4)$$

and for quadruplets, the analogous formula is:

$$\widehat{OR} = (3f_{10}+2f_{11}+f_{12})/4 \;/\; (3f_{03}+2f_{02}+f_{01})/4 \qquad (5)$$

An overall point estimate of the odds ratio may be obtained by summing the numerators of Equations 2-5 over all values of R (the matching ratio) and dividing by the sum of the denominators of Equations 2-5 (104).

The test statistic used for evaluating the null hypothesis, H_0: $\widehat{OR}$=1, was the Mantel-Haenszel chi-square, with 1 degree of freedom, and test-based confidence intervals were constructed where appropriate (see Appendix B). For the present study, all matched groups odds ratios, chi-square test statistics, and confidence intervals were computed by use of a program developed by OHSG personnel and based on formulae originally given by Mantel and Haenszel (104) and Miettinen (102).

Both Mantel-Haenszel matched sample and crude estimates of the odds ratio for cases compared to controls were computed for each OTG. Three minimum duration of OTG-specific employment criteria were considered for defining exposure:

1. exposed = worked for 15 or more days in the OTG of interest;

   not exposed = never worked in the OTG of interest or worked for fewer than 15 days.

2. exposed = worked for 2 or more years in the OTG of interest;

   not exposed = never worked or worked for fewer than 2 years in the OTG of interest.

3. exposed = worked for 5 or more years in the OTG of interest;

   not exposed = never worked or worked for fewer than 5 years in the OTG of interest.

All subjects must be classified according to exposure into dichotomous exposure categories in order to perform a matched analysis. For comparing "unexposed" subjects with those exposed for 2 or more years (or 5 or more years), two alternatives for classifying subjects as "unexposed" were considered: (1) subjects who worked in the OTG of interest for fewer than 2 years (or 5 years) were classified as not exposed and included in subsequent analyses; (2) subjects who worked in the OTG of interest for some period of time that was less than 2 years (or 5 years) were excluded from consideration, and OTG-specific odds ratios were based on subjects who were either never employed (not exposed) or employed for 2 or more (or 5 or more) years (exposed) in the OTG of interest.

For most analyses involving computation of odds ratios for more than one duration of employment category, both of these approaches were used. The effects of including in the not exposed categories workers having short-term exposures were evaluated by comparing results obtained by application of the two above exposure classification methods for the 2+ years and 5+ years minimum duration of employment categories. It was expected that exclusion of workers having relatively short-term exposures would reduce the possibility of obtaining diluted risk estimates. For example, in deriving risk estimates for OTG-specific exposures of 2+ years, classifying cases who were employed in the OTG of interest, but for fewer than two years, as not exposed would bias the odds ratio downward; classifying as not exposed controls having this same exposure history would bias the odds ratio upward. Alternatively, if the null hypothesis that duration of exposure is the same for cases and controls is true, odds ratio estimates should not be biased in either direction:

i.e., cases and controls having shorter duration of employment in the OTG of interest than required by the criterion should be classified as not exposed with the same frequency. If the alternative hypothesis is true that length of service in a particular OTG was longer for cases than for controls, controls would tend to be classified as not exposed more frequently than will cases, and the association between lung cancer mortality and exposure would appear to be stronger.

Although the design of the study minimizes differences between cases and controls in duration of overall rubber industry employment, it is possible that considerable differences between the amount of time spent by cases and controls in each OTG are present. For example, while the proportion of cases and controls employed in a given OTG for 2 or more years may have been the same and the resulting crude odds ratio equal to 1, the cases falling in this minimum duration of employment category may have had a mean work duration in the OTG of 10 years, while the controls may have spent only 3 years, on the average, in the same OTG. Such differences may be biologically meaningful, since duration of exposure is often considered to be a correlate of dose, and should be detected. Therefore, the mean cumulative duration of employment in each OTG was calculated separately for cases and controls who spent at least 1 month in the OTG of interest, and differences in means were evaluated with the two-sample t-test.

In order to take into account the latent period associated with lung cancer development, year of first employment in each OTG was considered. Crude odds ratios were computed for each OTG, with exposure defined as follows:

1. exposed = employed for at least 1 month in the OTG of interest and first employed there 15 or more years prior to death;

   not exposed = employed in the OTG of interest < 1 month or first employed there fewer than 5 years prior to death.

2. exposed = employed in the OTG of interest 2+ years and first employed there 15 or more years prior to death;

   not exposed = employed in the OTG of interest < 1 month or first employed there fewer than 5 years prior to death.

3. exposed = employed in the OTG of interest 5+ years and first employed there 15 or more years prior to death;

   not exposed = employed in the OTG of interest < 1 month or first employed there fewer than 5 years prior to death.

The three resulting sets of odds ratios are thus based on allowances in the exposure definitions for increasing lengths of employment in each OTG and for a 15 year latent period.

Also, for each OTG the mean year of first employment in the OTG was computed for cases and controls who had worked in the OTG for $\geq$ 1 month, 2+ years, and 5+ years. These means were compared, and differences were evaluated by the two-sample t-test.

CHAPTER V

RESULTS AND DISCUSSION

A. Results of the matching procedure

The one hundred thirty-one lung cancer deaths occurring among white male hourly rubber workers between January 1, 1964, and December 31, 1973, were matched with 500 controls on year of birth (± 3 years) and year of entry into the rubber industry (± 1 year). As indicated in Table 7, 10 cases and 52 controls were subsequently excluded from the study. Table 8 gives reasons for exclusions of initially selected study subjects. One case was eliminated when no suitable control could be found. Nine cases and 23 controls were excluded because work history information either was not available or was inadequate. An additional 26 controls were eliminated as the result of the withdrawal of their respective cases, and 3 controls both had missing work history information and had their respective case excluded.

Therefore, study results are based on 121 cases and 448 controls. The configurations of the 121 matched groups are summarized in Table 9. After exclusions, there were 94 quintuplets, 21 quadruplets, 4 triplets, and 2 pairs.

B. Comparability of study subjects with respect to control variables

Certain characteristics of the case series and the control group are presented in Table 10. As a group, cases and controls tended to have been born around 1900-1901, to have started working at the plant under study in 1930, and to have been about 29 years of age when initially employed. It is evident that the matching procedure was effective in

minimizing differences between cases and controls for these variables. Although the variations observed are slight, some of them are statistically significant, probably because of the large sample size involved.

It should be noted that consideration of mean year of first hire - 1931 for cases and 1930 for controls - is somewhat misleading in terms of describing this aspect of employment history. Examination of the frequency distributions of year of first hire given in Table 11 reveals that large proportions of both cases and controls entered the industry before 1930 and after 1940, while relatively few study subjects were hired during the 1930's. This hiring pattern was probably the result of reductions of the rubber industry production activities that occurred during the economic depression of the 1930's. Inspection of the frequency distributions presented in this table further confirms that cases and controls entered the industry during similar epochs.

As indicated in Table 10 the mean difference between cases and their respective controls in duration of overall employment is not significant ($p > 0.3$). Furthermore, examination of the frequency distribution of duration of overall employment for cases and controls given in Table 12 also fails to reveal any substantial differences in length of cumulative employment. 85.1% of the cases, compared to 85.5% of the controls were employed for 20 or more years. The fact that cases and controls worked, on the average, for the same amount of time suggests that cases and controls had equivalent opportunity for OTG-specific employment. The importance of this comparability with respect to the validity of the work history-related analyses carried out in this study was discussed in detail in Chapter IV.

As previously mentioned, all subjects included in the present study were members of the 1964 Cohort of rubber workers. Most former employees, included in this cohort, worked for more than 10 years. Therefore, it was expected that the percentage of short-term workers (those having fewer than 10 years of employment) among both cases and controls would be small. Furthermore, cases and controls were matched on year of birth and year of first hire at the plant under study, these matching criteria resulted in corresponding similarity between cases and controls in age at first hire. Thus, if most workers continued their employment at the plant until retirement at age 65 and if no strong respiratory carcinogen were present in the work environment, causing exposed workers to die of lung cancer before retirement, cases and controls should have had the same duration of employment.

Two possible alternative implications of the observed similarity between cases and controls in length of overall employment must be considered:

(1) No potent lung carcinogen was present in the work environment. Therefore, both cases and controls tended to work until retirement age. Since the matching scheme used in this study insured that they were approximately the same ages at first hire, cases and respective controls had the same duration of employment.

(2) A potent carcinogen was present, causing exposed workers to die of lung cancer soon after initiation of exposure. Then, because workers employed for fewer than 10 years may not have been included in the present investigation, the elevated risk for these short-term workers could not be detected. In order for this alternative to be plausible, one must hypothesize that a carcinogen, potent

enough to cause rapid development of lung cancer and concomitant termination of employment within 10 years of intial exposure, was present. The existence of such a strong carcinogen seems unlikely. Furthermore, reported latent periods for lung cancer resulting from exposures to industrial carcinogens are usually greater than 15 years (see Table 1, page 19).

It is clear that, for workers included in the present study, there is no association between duration of cumulative rubber industry employment and risk for lung cancer mortality. However, it should be emphasized that this study was not intended to evaluate the possibility of such an association, and, as noted above, efforts were made in designing the study to insure comparability between cases and controls in length of employment for the purpose of achieving valid estimates of OTG-specific risk for lung cancer.

C. Place of Birth

Place of birth distributions for cases and controls are given in Table 13. 11.5% of the cases were foreign-born, compared to 11.4% of the controls. There is, therefore, essentially no difference in proportion of cases and controls who were born in foreign countries. This fact suggests that there is no association between lung cancer mortality and foreign immigrant status in the population of rubber workers studied.

Table 14 gives place of birth distributions for cases and controls born in the United States. A higher proportion of cases than of controls (34.9%, compared to 23.6%) was born in southern states, while a higher proportion of controls (18.3%, compared to 13.2% for cases) was born

It would be of interest in subsequent studies of rubber industry workers to examine in detail the distribution of southern-born workers according to work area, in order to determine whether the second mechanism mentioned above may have had an impact on patterns of OTG-specific lung cancer risk. The possibility that southern migrant status may be a confounder of observed associations between work history and lung-cancer risk should also be considered.

D. Results of OTG-specific analyses

Table 17 gives the number and percentages of lung cancer cases and controls employed in each of the 20 OTG's for at least one month. Higher proportions of cases than of controls were employed in the following OTG's: Milling (2), Extrusion (3), Calendering (4), Stock Preparation (5), Reclaim Operation (14), Chemicals (15), Pliofilm Manufacture (16), and Special Products Manufacture (19). The proportions of cases employed in Compounding and Mixing (1) and in Curing (9) are slightly less than the corresponding proportions of controls. With regard to the remaining OTG's, the proportions of cases and controls are either equal, or the proportion of controls exceeds that of cases. The largest differences are observed for Milling (2), Extrusion (3), and Special Products Manufacture (19), all of which showed a higher proportion of cases than of controls employed for a least one month. For Extrusion (3), the difference is statistically significant at the 0.05 probability level. None of the remaining observed differences approaches statistical significance.

No case or control was employed in OTG 20. Therefore, no further reference to this OTG will be made.

The numbers and percentages of lung cancer cases and controls employed in each OTG for a minimum of two years are given in Table 18. As in the preceding table, the proportions employed in Compounding and Mixing (1) and in Curing (9) are essentially equal for cases and controls. The elevation in proportion of cases employed in Extrusion (3) observed in Table 17 is not noted for those who worked for at least two years. In addition, the small positive differences between proportion of cases and controls employed in Milling (2), Calendering (4), and Stock Preparation (5) are either reduced or absent for those employed for two or more years. This indicates that cases who contributed to the elevated proportions seen in Table 17 were employed in these OTG's for fewer than two years. The previously noted elevated proportions of cases employed in Reclaim Operation (14) and in Special Products Manufacture (19) are again observed in Table 18. For Chemicals (15) and Pliofilm Manufacture (16), the proportion of cases employed remains higher than that of controls. The greatest positive differences are observed for Reclaim Operation (14) and Special Products Manufacture (19). However, none of the differences in proportions reported in this table is statistically significant.

The number and percentages of cases and controls employed for five or more years are given for each OTG in Table 19. Compounding and Mixing (1) and Curing (9) show only slight differences in proportions of cases and controls employed. For Extrusion (3), the proportion of cases employed for five or more years is again greater than the proportion of controls. However, the numbers of cases and controls who worked in OTG 3 for at least five years are small, and the observed difference in

proportions is not statistically significant. The proportion of cases (9.1%) employed in Reclaim Operation (14) is more than twice that of controls (4.2%). This difference is statistically significant (p=0.04). Consistent elevations in proportions of cases, compared to controls, are observed for Chemicals (15), Pliofilm (16), and Special Products Manufacture (19). For these OTG's fewer subjects were employed for five or more years, and the magnitude of differences in proportions is reduced, relative to those observed in Tables 17 and 18.

Relative risk estimates (odds ratios) for each OTG and for three minimum duration of OTG-specific employment are given in Table 20. The odds ratios may be considered "crude", in the sense that they are derived without consideration of the matching procedure. For the purpose of computing these risk estimates, workers who fulfilled the stipulated minimum duration of employment criterion were regarded as exposed, while those who worked in the OTG of interest for any amount of time less than that given by the criterion were classified as not exposed. Thus, the comparisons on which the odds ratios given in this table are based are analogous to those made in Tables 17, 18, and 19. The observed results and tests of significance are also equivalent.

Most of the odds ratios in Table 20 cluster around unity, indicating an absence of association between a history of employment in the OTG of interest and risk for lung cancer. As expected on the basis of comparisons of proportions of exposed cases and controls and tests made for Tables 17, 18, and 19, the only odds ratios that are statistically significantly elevated above one are those for Extrusion (3) for exposures of at least one month and for Reclaim Operation (14) for exposures of 5+ years.

Also, for the latter OTG, the odds ratio increases from 1.3 (exposure $\geq$ 1 month), to 1.7 (exposure $\geq$ 2 years), to 2.3 (exposure $\geq$ 5 years), suggesting a possible association between both occurrence and duration of employment in this OTG. For Compounding and Mixing (1) and Curing (9), the odds ratios are uniformly close to one.

The computation of the risk estimates reported in Table 21 differs from the procedure used for the odds ratios in Table 20 as follows: each odds ratio in Table 21 is based on comparison of those designated as exposed by the minimum duration of employment criterion with those never employed in the OTG of interest or employed cumulatively for less than one month. Comparison of those classified as exposed with workers never employed or employed in the OTG of interest for less than one month, rather than with subjects who may have worked for longer amounts of time, reduces the possibility of obtaining diluted risk estimates.

Most of the odds ratios in Table 21 are close to one, again indicating no association between employment in the OTG of interest and risk for lung cancer. The odds ratio of 1.6 for those employed in Extrusion (3) for at least one month, compared to workers employed for less than one month, represents a statistically significant elevation in risk. The odds ratio is also elevated for those employed in Extrusion for 5+ years, but this elevation is not significant. For Reclaim Operation (14), the odds ratio again increases from 1.3 for those employed $\geq$ 1 month, to 1.7 for those employed 2+ years, to 2.2 for those employed for at least five years. The latter estimate is statistically significantly elevated above unity ($X^2=4.24$, $p=0.04$). Finally, consistently elevated risk estimates are observed for Chemicals (15), Pliofilm (16), and

Special Products Manufacture (19), although none of these achieved statistical significance. It does not appear that the risk estimates given in Table 20 for the 2+ and 5+ years minimum duration of employment classifications are biased towards the null by inclusion among the non-exposed of workers having >1 month of employment.

Mantel-Haenszel odds ratios for matched groups data are given in Table 22. In this table, risk estimates are based on exposed defined as employed in the OTG of interest for the amount of time stipulated by the minimum duration criterion, and not exposed defined as employed for any period of time less than that given by the criterion of interest. The odds ratio for Reclaim Operation (14), for those employed for at least five years, is 2.2 (X^2=4.52, $p < 0.05$), and for Special Products Manufacture (19), for those ever employed, the odds ratio is 1.7 (X^2=4.77, $p < 0.05$). None of the other odds ratios included in this table is statistically significant at the 0.05 probability level. However, odds ratios having a 90% confidence interval with a lower limit that is greater than one are observed for the following OTG's: Extrusion (3), for exposures of any duration and of 5+ years; Pliofilm (16), for exposures of any duration; and Special Products Manufacture (19), for exposures of 2+ years. For Reclaim Operation (14), the tendency for the magnitude of the odds ratio to increase with increments in the minimum duration of employment criterion is again apparent.

Because the definition of non-exposed for odds ratios given in Table 22 may include in this category subjects who worked in the OTG of interest, the observed risk estimates may be somewhat conservative as noted also for the analyses presented in Table 20. For this reason, Mantel-Haenszel odds ratios, with exposed defined as employed in a given OTG for two or more years or for five or more years, and not exposed

defined for each duration of employment category as never employed in the OTG, were derived. These are shown in Table 23. These estimates are based on smaller numbers of cases and controls, since all subjects not falling precisely into either the "exposed" or the "not exposed" categories were excluded from the analysis. For example, in computing the odds ratio for Extrusion (3), 5+ years of employment, all subjects employed in this OTG for one month through four years were excluded. Examination of the odds ratios in this table does not suggest that the estimates reported in Table 22 are biased towards the null.

As explained in Chapter IV, it was expected that the crude odds ratios, which ignore the matching procedure employed in this study, would be biased towards the null with respect to the Mantel-Haenszel odds ratios, which take the matching into account. It is apparent from comparisons of results given in Tables 20 and 21 with those given in Tables 22 and 23 that this bias, in terms of both efficiency and magnitude of observed point estimates, is either slight or absent. For example, in Table 21 the crude odds ratio for Reclaim Operation (14), for exposure of 5+ years, is 2.2 (X^2=4.24). In Table 23, the Mantel-Haenszel point estimate is 2.1 (X^2=3.31). This lack of bias towards the null suggests that exposure (i.e., OTG-specific employment) and the matching variables are not highly correlated. However, because the matching procedure was necessary in order to insure equal opportunity for OTG-specific employment during comparable time periods for cases and controls, the Mantel-Haenszel odds ratios derived through stratified analysis based on the matched groups confirm the validity of the crude risk estimates given in Tables 20 and 21.

Table 24 gives crude odds ratios, with exposure defined by three minimum duration of employment criteria and an allowance for a 15-year latent period. These risk estimates differ from those computed for preceding tables as follows:

(1) all subjects who worked for at least one month in a given OTG but who were first employed in the OTG 5 through 14 years prior to death were excluded from the analyses;

(2) all subjects who worked for less than one month or who worked for up to five years in the OTG of interest but who were first employed there fewer than five years prior to death were considered as not exposed.

Thus, exposed subjects for each minimum length of employment category must have started working in the OTG at least 15 years before year of death. Comparisons of odds ratios given in this table with those shown in Table 21 indicate the following:

(1) for Extrusion (3), for the $\geq$1 month category, the odds ratio decreases from 1.6 (Table 21, no allowance for latent period) to 1.4 (Table 24, 15-year latent period stipulation). The observed decrease occurred because of the exclusion from the latter analysis of seven cases who were first employed in Extrusion 5 to 14 years prior to death. Twenty-two controls were excluded for the same reason. In addition, two controls who first started working in OTG 3 fewer than five years prior to death were reclassified as not exposed for the analysis presented in Table 24. Computation of a risk estimate, basing the exposure definition on a latent period allowance of five or more years, instead of 15 or more years, results in an odds ratio of 1.7 (X^2=4.37, p=0.05). For the five

year minimum duration of employment category, the odds ratio increases from 2.0 (Table 21) to 2.3 (Table 24). The observed increase occurred as the result of the elimination of six controls who had five or more years of experience in Extrusion but who first started working there 5-14 years before death. As expected, no cases or controls were reclassified as not exposed for this length of employment category.

(2) for Reclaim Operation (14), for the $\geq$1 month category, the point estimate of the odds ratio decreases from 1.3 (Table 21) to 1.2 (Table 24). This slight decrease occurred because of the exclusion of two cases, compared to one control, who started working in Reclaim (14) 5 through 14 years before death. In addition, one control who was first employed in OTG 14 within five years prior to death was reclassified as not exposed. For the 2+ years category, the odds ratio remains unchanged. For the 5+ years duration of employment category, the odds ratio increases from 2.2 (Table 21) to 2.5 (X^2=5.37, p=0.02) (Table 24). One control, first employed in Reclaim 5-9 years prior to death, was excluded. No case was eliminated or reclassified with respect to exposure status.

(3) for Special Products Manufacture (19) for the 2+ years minimum duration of employment category, the odds ratio increases from 1.7 (Table 21) to 1.8 (Table 24). Four controls and one case who started working 5 through 14 years before death were excluded. In addition, four controls who worked for two or more years but who were first employed in OTG 19 fewer than five years prior to death were classified as not exposed.

(4) with regard to other OTG's, allowance for a 15-year latent period does not result in marked changes in risk estimates. In no instance does the consideration of a 15-year latent period lead to the emergence of an association not already indicated by previous analyses conducted in this study.

It was not possible to carry out separate analyses, based on odds ratios, for mutually exclusive categories of latent periods shorter than 15 years, because of small numbers of subjects classified as exposed in such categories.

In order to ascertain whether or not there were differences between cases and controls with respect to the years in which they were first employed in given OTG's the mean year of first employment in each OTG for those who worked for ≥1 month, 2+ years, and 5+ years were computed and are reported in Tables 25, 26, and 27. For Extrusion (3), cases started work within two years of controls, on the average. For Reclaim Operation (14), cases were first employed, on the average three years (for the ≥1 month and 2+ years categories) to five years (for the 5+ years category) before controls. The observed differences in mean year of first employment in OTG 14 are not statistically significant. For Curing (9), cases were first employed, on the average, four years (for the ≥1 month duration of employment category) to seven years (for the 2+ and 5+ years categories) before controls. For those who worked for at least two years and for at least five years, the differences in mean year of initial employment in OTG 9 is statistically significant at the 0.05 probability level. Finally, for OTG 15 (Chemicals), cases started working, on the average 4-7 years later than controls. Apparently, cases tended to have been first employed in OTG 15 in the late 1940's or early 1950's, while controls tended to have started working in this OTG in the mid 1940's.

The implications of the above observed differences in mean years of initial employment in Curing (9), Reclaim Operation (14), and Chemicals (15) cannot be objectively determined. However, the existence of such differences suggests that the exposure experiences of cases may have differed qualitatively and/or quantitatively from those of controls, since they were employed, at least in part, during different calendar periods.

Table 28 gives mean durations of employment for each OTG for cases and controls having at least one month of experience in the OTG of interest. Although none of the differences in means observed is statistically significant, it should be noted that cases' mean length of employment in Reclaim Operation (14) was nearly twice that of controls - 11.2 years for cases, compared to 5.7 years for controls. This information may be interpreted as further evidence for an association between a history of employment in this OTG and risk for lung cancer. Other OTG's in which cases spent a greater number of years than controls include Extrusion (3), Curing (9), Finishing, Inspection and Repair (10), Synthetic Latex Manufacture (17), and Metal Products (18).

E. Summary of results of the OTG-specific analyses

The major findings of the OTG-specific analyses conducted in this study are summarized in Tables 29, 30, and 31. The Mantel-Haenszel odds ratios given in these tables are reported in Table 22.

Compounding and Mixing (OTG 1) and Curing (OTG 9)

The Mantel-Haenszel odds ratios for Compounding and Mixing (1) and for Curing (9) presented in Table 29 are uniformly close to unity and indicate that the exposure rates for these two work areas were the same

or lung cancer cases and controls and, hence, that, for the population of rubber workers studied, there is no association between risk for lung cancer and a history of employment in either of these work areas. Thus, the current investigation fails to replicate findings of an association between increased risk, for lung cancer and employment in jobs involving the compounding and mixing and curing of rubber previously reported in the literature (4-10).

Several plausible reasons for discrepancies across studies in findings regarding the risk indicator status of the compounding and mixing and curing work areas may be advanced. First, potential exposures in the work areas designated as compounding and mixing and curing may not have been comparable for all rubber worker populations considered in the various studies. The compounding and mixing and curing work areas involve the potential for exposure to respiratory hazards at most rubber plants by virtue of the fact that known respiratory system irritants and, perhaps, carcinogens were used in processes carried out in these areas. For compounding and mixing, respiratory hazards include pulmonary irritants such as zinc oxide, zinc stearate, carbon black, talc, and phenols and, possibly, carcinogens such as cadmium compounds (used as accelerators) and chromates present in pigments. For curing, potential exposures are to talc and phenol-formaldehyde resins, and to unknown reaction products present in curing fumes. However, there are no available environmental data indicating that the intensity of use of these materials was the same at all rubber plants studied; nor is there any information regarding possible differences in industrial hygiene practices and environmental control measures at the various plants. Variation in these factors could have influenced risk for lung cancer.

Second, controls for the present study were selected from among deaths, including all deaths due to other malignancies, and 76 deaths due to cancers other than lung cancer were accordingly chosen as controls. Fifteen of these were deaths due to prostate cancer and 4, to stomach cancer. Associations with a history of employment in compounding and mixing for cancer of the prostate and in OT's involving high talc exposure for cancer of the stomach have recently been reported (OHSG, unpublished). Therefore, inclusion of subjects who died of these malignancies in the control group for the present study may have biased effect measures for Compounding and Mixing towards the null. Future investigations of this work area, if conducted in the case-control mode, should exclude from the control group workers who died of these malignancies. Also, it should be noted that, if some other cause of death (cardiovascular disease, for example) were associated with a history of employment in either Compounding and Mixing or Curing in the control group used in the present study, the effect measures for these OTG's would, again, be conservative.

Third, the risk estimates for compounding and mixing and curing reported by previous studies may have been spuriously elevated, and the indicated associations may have been due either to chance or to the differential exposure of subjects employed in these two work areas to other risk factors, such as cigarette smoke. Several important non-occupational risk factors for lung cancer (potential confounders) were not controlled for in the present or in previously reported studies.

Reclaim Operation (OTG 14)

Mantel-Haenszel odds ratios for Reclaim Operation (OTG 14) are summarized in Table 30. The observed risk estimates are consistently elevated above unity and increase with each increment in the minimum duration of employment exposure criterion. These odds ratios suggest that risk for lung cancer is associated both with the occurrence of employment in Reclaim Operation and with length of employment in this work area. The minimum duration of employment classifications do not, however, permit assessment of possible dose-response relationships, since exposure categories are not mutually exclusive. Among the 18 cases and 54 controls employed in Reclaim Operation for at least 1 month (see Table 22), mean duration of employment in this OTG was nearly two times longer for cases than for controls, and cases, on the average, were first employed in Reclaim Operation three years before controls. Thus, since duration of employment may be a correlate of dose and since changes in industrial hygiene practices may have resulted in improvements in exposure conditions over time, these latter two findings suggest that cases who worked in Reclaim Operation may have sustained heavier exposures to respiratory system hazards present in this OTG than controls. Respiratory system hazards are numerous in Reclaim Operation and include potential heavy exposures to particulates released during the process of shredding scrap rubber products, to chemicals and oils added to the shredded rubber during devulcanizing, and to fumes from heated rubber emitted during milling.

For exposures defined as 5 or more years of employment in Reclaim Operation, the 95% confidence interval (1.06, 4.57) of the odds ratio does not include one. Therefore, it is unlikely that the suggested

association between a history of employment in Reclaim Operation and elevated risk for lung cancer is due to chance.

It should be noted that McMichael et al. (10) also detected the presence of an association between employment in the Reclaim work area and death due to malignancies of the respiratory system. The relative risk reported by the latter investigators was 2.3 for workers having at least 5 years of exposure to Reclaim. This risk estimate suggests that the magnitude of the association observed for Reclaim was similar to that noted in the present study ($\hat{OR}$ = 2.2 for those employed 5+ years).

Chemicals (OTG 15), Pliofilm (OTG 16), and Special Products Manufacture (OTG 19)

Mantel-Haenszel odds ratios for Chemicals (15), Pliofilm (16), and Special Products Manufacture (19) are summarized in Table 31. For these OTG's, point estimates of relative risk were consistently elevated above one for each minimum duration of employment category. However, there is no evidence suggesting an association between duration of employment in these OTG's and risk. The mean duration of employment in each of the OTG's mentioned in this table is approximately equal for cases and controls (see Table 28). Cases started working later than controls, indicating the possibility of differential exposures for cases and controls employed in these OTG's. With the exception of the risk estimate ($\hat{OR}$ = 1.7) for Special Products Manufacture (19), for those ever exposed, the odds ratios for these OTG's are not statistically significantly elevated. The numbers of workers employed in these OTG's are small, and the observed associations may have been due to chance. However, the possible excess in lung cancer risk for workers employed in Chemicals, Pliofilm, and Special Products Manufacture should be investigated further, and attempts should be made to identify agents, if any, present in these areas and having potential etiologic significance.

Tubes (OTG 6) and Product Fabrication (OTG 7)

Finally, it should be noted that the odds ratios for Tubes (OTG 6) were 0.5 and 0.6 for those employed for 2+ and 5+ years, respectively. The Tube OTG includes jobs entailing potentially heavy exposures to talc. It has been suggested that workers exposed to industrial grades of talc may sustain an elevated risk for lung cancer mortality (66). However, the absence of an association between increased risk for lung cancer and a history of employment in Tubes in the present study does not support this hypothesis. Two explanations for this finding may be advanced:

(1) Workers with a history of employment in Tubes tended to die of exposure-related causes other than lung cancer (e.g., chronic respiratory diseases).

(2) Workers employed in Tubes tended to reduce their cigarette consumption, perhaps because of high levels of respiratory system irritants present in this work area. If talc does not contain respiratory carcinogens and is not a sufficient cause of lung cancer but, rather, contributes to the etiology of this disease only in the presence of carcinogens or cocarcinogens (such as those contained in cigarette smoke), then the risk for lung cancer would have been low for workers in Tubes. It is not possible to evaluate the correctness of either of these assumptions in the present study.

The Product Fabrication OTG (OTG 7) includes tire building jobs. Odds ratios for this OTG, reported in Table 22, are 0.7 and 0.8 for those employed for 2+ and 5+ years, respectively. Thus, the findings of the present study are not indicative of an elevated lung cancer risk for workers engaged in tire building. Such an association was reported by Mancuso (7) but has not been noted by other investigators (9,10,84).

Table 7

Results of the Matching Procedure
for the Rubber Worker Lung Cancer Case-Control Study

	Total	Cases	Controls
Number of subjects originally selected	631	131	500
Number of subjects excluded	62	10	52
Total number included	569	121	448

Table 8

Selection of Rubber Worker Lung Cancer
Case-Control Study Subjects:
Reasons for Exclusions

	Reason for Exclusion	Number Excluded
Cases:		
	No acceptable match found	1
	Missing or incomplete work history	9
	Total number excluded	10
Controls:	Respective case excluded	26
	Missing or incomplete work history	23
	Both of the above reasons	3
	Total number excluded	52

Table 9

Results of the Matching Procedure
for the Rubber Worker Lung Cancer Case-Control Study:
Configurations of Matched Groups

Group Configuration	(Number of controls per case)	Number of Groups Before Exclusions	Number of Groups After Exclusions
Quintuplets	(4)	121	94
Quadruplets	(3)	2	21
Triplets	(2)	4	4
Pairs	(1)	2	2
No Match	(0)	2	-
Total		131	121

Table 10

Selected Characteristics of Lung Cancer Cases and Controls

Characteristic	Cases Group Mean (S.D.)	Controls Group Mean (S.D.)	Mean Paired Difference (S.E.(D))		t_{120}
Age at Death	67.3 (8.9)	69.8 (8.8)	-2.47	(0.15)	-16.8#
Duration of Overall Employment (yrs.)	29.4 (9.3)	29.9 (9.2)	-0.19	(0.48)	- 0.4
Year of Birth	1901 (8.8)	1900 (8.6)	0.91	(0.10)	*
Year of 1st Hire	1931 (11.8)	1930 (11.7)	0.09	(0.04)	*
Age at 1st Hire	29.1 (9.2)	29.7 (9.1)	-0.88	(0.11	- 7.8#

*Matching variable.
#$p < 0.05$

Table 11

Frequency Distribution of Year of First Hire
for Lung Cancer Cases and Controls

Year of First Hire	Cases		Controls	
	Number	(%)	Number	(%)
<1910	1	(0.8)	2	(0.4)
1910-19	29	(24.0)	117	(26.1)
1920-29	39	(32.2)	146	(32.6)
1930-39	5	(4.1)	12	(2.7)
1940-49	44	(36.4)	166	(37.1)
1950-54	3	(2.5)	5	(1.1)
All	121	(100.0)	448	(100.0)

Table 12

Frequency Distribution
of Duration of Rubber Industry Employment
for Lung Cancer Cases and Controls

Duration of Employment (yrs)	Cases		Controls	
	Number	(%)	Number	(%)
<10	0	(0)	4	(0.9)
10-14	6	(5.0)	12	(2.7)
15-19	12	(9.9)	49	(10.9)
20-24	32	(26.4)	90	(20.1)
25-29	13	(10.7)	72	(16.1)
≥30	58	(47.9)	221	(49.3)
All	121	(99.9)	448	(100.0)
≥20	103	(85.1)	383	(85.5)

Table 13

Place of Birth Distribution
for Rubber Worker Lung Cancer Cases and Controls

Place of Birth	Cases		Controls	
	Number	(Per cent)	Number	(Per cent)
U.S.A.	106	(87.6)	395	(88.2)
Foreign	14	(11.5)	51	(11.4)
Unknown	1	(0.8)	2	(0.4)
Totals	121	(100.0)	448	(100.0)

Table 14

Place of Birth Distribution
for Native-Born Rubber Worker Lung Cancer
Cases and Controls

Place of Birth	Cases		Controls	
	Number	(Per cent)	Number	(Per cent)
Ohio	29	(27.4)	121	(30.7)
Southern States[1]	37	(34.9)	93	(23.6)
Northeastern States[2]	14	(13.2)	72	(18.3)
Other U.S.[3]	26	(24.5)	108	(27.4)
Totals	106	(100.0)	397	(100.0)

[1]Includes the following states: Ky., Tenn., Ga., Ala., La., Ark., Miss., Va., N.C., S.C., Fla., Md., Tex., Okla.

[2]Includes the following states: Pa., N.J., N.Y., Conn.

[3]Includes the following states: W. Va., Ind., Ill., Nebr., Mich., Kan.

Table 15

Place of Birth:
Chi-Square Test of Association,
Southern States vs. All Other
Places of Birth

Place of Birth	Cases N	Cases (%)	Controls N	Controls (%)	Total
Southern States	37	(30.6)	93	(20.8)	130
All Other	84	(69.4)	355	(79.2)	439
Total	121	(100.0)	448	(100.0)	569

$X^2_{1\ d.f.} = 5.2114;\ p < 0.025$

Table 16

Place of Birth:
Chi-Square Test of Association,
Northeastern States vs. All
Other Places of Birth

Place of Birth	Cases N	Cases (%)	Controls N	Controls (%)	Total
Northeastern States	14	(11.6)	72	(16.1)	86
All Other Places	107	(88.4)	376	(83.9)	483
Total	121	(100.0)	448	(100.0)	569

$X^2_{1\ d.f.} = 1.5045,\ p > 0.20$

Appendix A-2 *

OT - OTG Dictionary

Occupational Title Group	Component OT's	OTG
1. Compounding and Mixing	001, 002, 003, 004, 005, 006, 007, 008, 060, 065, 078, 083	1
2. Milling	009, 010, 011, 012, 013, 079, 084	2
3. Extrusion	019, 021, 023, 024, 025	3
4. Calendering	014, 015, 016	4
5. Stock Preparation	017, 018	5
6. Tubes	020, 022, 031, 032, 034, 042	6
7. Product Fabrication	026, 027, 028	7
8. Curing Preparation	029, 030	8
9. Curing	033, 035, 036, 037, 038, 080, 085	9
10. Finishing, Inspection & Repair	040, 041, 043, 081, 086	10
11. Maintenance	039, 044, 045, 046, 047, 048, 049, 050, 051, 052	11
12. General Service	053, 054, 055, 056, 057, 059, 082, 088	12
13. Shipping & Receiving	058	13
14. Reclaim Operation	061, 062, 063, 064	14
15. Chemicals	066, 067, 068, 069, 070, 072, 073, 074, 09	15
16. Pliofilm Manufacture	075, 076, 077	16
17. Synthetic Latex Manufacture	089, 090, 091	17
18. Metal Products	092, 093, 094, 095, 099, 100	18
19. Special Products Manufacture	071, 087, 097, 098	19
20. Miscellaneous	111, 112, 113, 114, 118, 119	20
21. Exit	101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 115, 116, 117	

*Appendix A-2 is reproduced here to facilitate interpretation of OTG codes.

Table 17

Number and Per Cent of Lung Cancer Cases and Controls Ever* Employed in each of 20 OTC's

OTG	Cases Number	(%)	Controls Number	(%)	Chi-square#
1	41	(33.9)	153	(34.2)	0.003
2	48	(39.7)	142	(31.7)	3.722 (p=.06)
3	30	(24.8)	76	(17.0)	3.852 (p=.05)
4	21	(17.4)	66	(14.7)	0.324
5	27	(22.3)	92	(20.5)	0.091
6	23	(19.0)	91	(20.3)	0.036
7	44	(36.4)	163	(36.4)	0,010
8	20	(16.5)	82	(18.3)	0.101
9	29	(24.0)	115	(25.7)	0.070
10	44	(36.4)	170	(37.9)	0.045
11	27	(22.3)	125	(27.9)	1.247
12	54	(44.6)	201	(44.9)	0.003
13	22	(18.2)	81	(18.1)	0.012
14	18	(14.9)	54	(12.1)	0.455
15	25	(20.7)	72	(16.1)	1.113
16	7	(5.8)	12	(2.7)	1.967
17	2	(1.7)	12	(2.7)	0.100
18	10	(8.3)	36	(8.0)	0.011
19	31	(25.6)	84	(18.8)	2.788 (p=.09)
20[¢]	0	(0.0)	0	(0.0)	-

*Employed cumulatively for $\geq$ 1 month.
#Chi-square with 1 d.f., for those employed, compared to those not employed in the OTC of interest.
¢Note: no subject was employed in OTC 20.

Table 18

Number and Per Cent of Lung Cancer Cases and Controls Employed for at Least 2 Years in each of 19 OTG's

OTG	Cases		Controls		Chi-square*
	Number	(%)	Number	(%)	
1	25	(20.7)	87	(19.4)	0.031
2	20	(16.5)	77	(17.2)	0.001
3	10	(8.3)	37	(8.3)	0.034
4	11	(9.1)	36	(8.0)	0.035
5	15	(12.4)	51	(11.4)	0.022
6	7	(5.8)	54	(12.1)	3.284
7	22	(18.2)	110	(24.6)	1.828
8	9	(7.4)	41	(9.2)	0.168
9	18	(14.9)	70	(15.6)	0.004
10	29	(24.0)	88	(19.6)	0.842
11	24	(19.8)	97	(21.7)	0.095
12	30	(24.8)	112	(25.0)	0.005
13	11	(9.1)	48	(10.7)	0.124
14	15	(12.4)	34	(7.6)	2.800
15	13	(10.7)	30	(6.7)	1.692
16	4	(3.3)	8	(1.8)	0.457
17	1	(0.8)	4	(0.9)	0.230
18	8	(6.6)	18	(4.0)	0.935
19	16	(13.2)	38	(8.5)	2.493

*Chi-square with 1d.f., for those employed 2+ years, com... to those employed for fewer than 2 years.

Table 19

Number and Per Cent of Lung Cancer Cases and Controls Employed for at Least 5 Years in each of 19 OTG's

OTG	Cases		Controls		Chi-square*
	Number	(%)	Number	(%)	
1	17	(14.0)	67	(15.0)	0.011
2	15	(12.4)	57	(12.8)	0.003
3	8	(6.6)	16	(3.6)	1.492
4	6	(5.0)	21	(4.7)	0.014
5	12	(9.9)	34	(7.6)	0.417
6	5	(4.1)	33	(7.4)	1.122
7	18	(14.9)	84	(18.8)	0.726
8	5	(4.1)	16	(3.6)	0.000
9	15	(12.4)	48	(10.7)	0.130
10	20	(16.5)	55	(12.3)	1.157
11	22	(18.2)	97	(21.7)	0.500
12	23	(19.0)	78	(17.4)	0.075
13	9	(7.4)	36	(8.1)	0.001
14	11	(9.1)	19	(4.2)	4.487 (p=.04)
15	7	(5.8)	21	(4.7)	0.067
16	3	(2.5)	6	(1.3)	0.232
17	1	(0.8)	3	(0.7)	0.185
18	5	(4.1)	13	(2.9)	0.155
19	4	(3.3)	10	(2.2)	0.120

*Chi-square with 1 d.f., for those employed 5+ years, compared to those employed for fewer than 5 years.

Table 20

Odds Ratios for Employment in 19 OTG's
by Three Minimum Duration of Employment Categories

OTG	Odds Ratios: Minimum Duration of Employment* Ever	2+ years	5+ years
1	1.0	1.1	0.9
2	1.4	1.0	1.0
3	1.6 #	1.0	1.9
4	1.2	1.1	1.1
5	1.1	1.1	1.3
6	0.9	0.4	0.5
7	1.0	0.7	0.8
8	0.9	0.8	1.2
9	0.9	0.9	1.2
10	0.9	1.3	1.4
11	0.7	0.9	0.8
12	1.0	1.0	1.1
13	1.0	0.8	0.9
14	1.3	1.7	2.3 #
15	1.4	1.7	1.2
16	2.2	1.9	1.9
17	0.6	0.9	1.2
18	1.0	1.7	1.4
19	1.5	1.6	1.5

*Any subject never employed in the OTG of interest or employed for a shorter period than that indicated by the minimum duration of employment criterion was considered "not exposed."

# $p < 0.05$

Table 21

Odds Ratios for Those Employed, Compared to Those Never* Employed, for 19 OTG's by Three Minimum Duration of Employment Categories

	Odds Ratios		
	Minimum Duration of Employment		
OTG	Ever#	2+ Years	5+ years
1	1.0	1.1	0.9
2	1.4	1.1	1.1
3	1.6 (X^2=3.9)¢	1.1	2.0
4	1.2	1.2	1.1
5	1.1	1.1	1.3
6	0.9	0.5	0.6
7	1.0	0.7	0.8
8	0.9	0.8	1.1
9	0.9	0.9	1.1
10	0.9	1.2	1.3
11	0.7	0.9	0.8
12	1.0	1.0	1.1
13	1.0	0.8	0.9
14	1.3	1.7	2.2 (X^2=4.2)¢
15	1.4	1.7	1.3
16	2.2	1.9	1.9
17	0.6	0.9	1.2
18	1.0	1.6	1.4
19	1.5	1.7	1.6

*Never, for each duration of employment category, is defined as zero or less than 1 month in the OTG of interest.

#Ever is defined as 1 or more months of employment in the OTG of interest.

¢$p < 0.05$.

Table 22

Odds Ratios for Matched Groups
for 19 OTG's by Three Minimum Duration of
Employment Categories

OTG	Odds Ratios Minimum Duration of Employmen Ever	2+ years	5+ years
1	1.0	1.1	0.9
2	1.3	1.0	1.0
3	1.6#	1.1	2.2#
4	1.2	1.2	1.1
5	1.0	1.1	1.4
6	1.0	0.5#	0.6
7	1.1	0.7	0.8
8	0.9	0.8	1.3
9	1.0	1.0	1.2
10	0.9	1.4	1.5
11	0.7	0.9	0.8
12	1.0	1.0	1.1
13	1.0	0.8	0.9
14	1.3	1.6	2.2#¢
15	1.3	1.7	1.3
16	2.5#	2.0	2.0
17	0.7	1.0	1.3
18	0.9	1.5	1.5
19	1.7#¢	1.7#	1.5

*Any subject never employed in the OTG of interest or employed for a shorter period than that indicated by the minimum duration of employment criterion was considered "not exposed."
#90% confidence limits do not include 1.
¢95% confidence limits do not include 1.

Table 26

Mean Year* of First Employment in 19 OTG's
for Cases and Controls Employed
for at Least 2 Years in the OTG of Interest

OTG	Mean Year of First Employment				t		OTG
	Cases	(S.D.)	Controls	(S.D.)			
1	1936	(10.4)	1939	(11.1)	-0.01		1
2	1936	(9.8)	1938	(10.9)	-0.64		2
3	1942	(9.5)	1940	(15.7)	0.51)		3
4	1938	(12.7)	1937	(13.2)	0.22		4
5	1935	(13.4)	1932	(12.1)	0.53		5
6	1928	(9.4)	1935	(11.2)	-1.83		6
7	1932	(10.9)	1931	(12.4)	0.23		7
8	1941	(13.4)	1942	(13.7)	-0.17		8
9	1926	(12.0)	1933	(12.3)	-2.34	($p<.05$)	9
10	1931	(15.1)	1934	(14.7)	-1.05		10
11	1939	(10.6)	1937	(12.5)	0.98		11
12	1936	(13.6)	1937	(13.3)	-0.37		12
13	1936	(10.4)	1940	(11.4)	-0.99		13
14	1933	(12.7)	1936	(12.2)	-0.88		14
15	1949	(6.2)	1945	(8.0)	1.62		15
16	1954	(6.2)	1948	(7.4)	1.48		16
17	-	-	1946	(14.8)	-		17
18	1943	(5.7)	1943	(6.6)	-0.06		18
19	1944	(5.1)	1943	(8.5)	0.36		19

*To the nearest year.

Table 27

Mean Year* of First Employment in 19 OTG's
for Cases and Controls Employed
for at Least 5 Years in the OTG of Interest

OTG	Mean Year of First Employment				t
	Cases	(S.D.)	Controls	(S.D.)	
1	1937	(10.4)	1935	(10.9)	0.78
2	1935	(10.6)	1936	(11.1)	-0.15
3	1939	(8.7)	1941	(16.8)	-0.23
4	1935	(13.1)	1935	(14.7)	0.06
5	1935	(14.0)	1932	(12.2)	0.57
6	1926	(10.5)	1931	(10.0)	-0.94
7	1930	(10.2)	1931	(12.5)	-0.39
8	1943	(12.9)	1935	(11.2)	1.22
9	1923	(11.2)	1930	(12.5)	-2.07 ($p<.05$)
10	1927	(12.8)	1933	(15.5)	-1.95 ($p<.10$)
11	1940	(10.3)	1937	(12.5)	1.23
12	1939	(12.8)	1937	(13.1)	0.61
13	1936	(11.4)	1938	(10.1)	-0.45
14	1932	(13.7)	1937	(12.9)	-1.12
15	1951	(5.7)	1944	(8.2)	2.40 ($p<.05$)
16	1956	(6.2)	1945	(5.2)	2.63
17	-	-	1953	(3.5)	-
18	1943	(3.1)	1943	(5.7)	0.03
19	1947	(6.7)	1941	(10.2)	1.36

*To the nearest year.

Table 28

Mean Duration of Employment in 19 OTG's for Lung Cancer Cases and Controls, Based on the Experience of Workers Having at Least 1 Month of Employment in the OTG's

OTG	Mean Duration of Employment (yrs.) Cases	Controls	t*
1	5.8	7.3	-1.59
2	5.4	6.4	-0.75
3	4.8	3.7	0.71
4	6.2	6.5	-0.13
5	7.4	8.0	-0.28
6	4.8	6.6	-0.80
7	7.1	9.9	-1.66
8	3.3	3.9	-0.59
9	9.7	7.8	0.87
10	7.5	5.6	1.35
11	17.1	18.2	-0.44
12	6.2	7.0	-0.67
13	6.7	7.6	-0.42
14	11.2	5.7	1.83
15	4.4	4.6	-0.14
16	4.7	6.3	-0.60
17	7.0	3.5	0.50
18	10.7	6.8	1.05
19	3.1	2.6	0.54

*Based on the comparison of group means; separate variance estimates.

Table 29

Summary of Mantel-Haenszel Odds Ratios
for Compounding and Mixing and Curing

OTG Duration of Employment	N of Cases Exposed	N of Controls Exposed	$\hat{OR}$	X^2	90% CI
Compounding & Mixing (OTG 1)					
Ever	57	159	1.0	0.045	(0.67,1.37)
2+ years	25	87	1.1	0.110	(0.70,1.73)
5+ years	17	67	0.9	0.049	(0.55,1.58)
Curing (OTG 9)					
Ever	29	129	1.0	0.033	(0.66,1.40)
2+ years	18	70	1.0	0.015	(0.58,1.62)
5+ years	15	48	1.2	0.312	(0.71,2.05)

Table 30

Summary of Mantel-Haenszel Odds Ratios
for Reclaim Operation (OTC 14)

Minimum Duration of Employment	N of Cases Employed	N of Controls Employed	OR	X^2	90% CI
Ever	21	58	1.3	1.139	(0.85,2.10)
2+ years	15	34	1.6	2.183	(0.95,2.66)
5+ years	11	19	2.2	4.522	(1.20,4.06)*

*95% confidence interval also does not include 1.

Table 31

Summary of Mantel-Haenszel Odds Ratios
for Chemicals (OTG 15), Pliofilm (OTG 16), and
Special Products Manufacture (OTG 19)

OTG Duration of Employment	N of Cases Employed	N of Controls Employed	OR	X^2	90% CI
Chemicals (15)					
Ever	25	74	1.3	0.997	(0.83,2.08)
2+ years	13	30	1.7	2.291	(0.96,3.30)
5+ years	7	21	1.3	0.284	(0.59,2.80)
Pliofilm (16)					
Ever	8	13	2.5	3.240	(1.08,5.94)
2+ years	4	8	2.0	1.170	(0.70,5.74)
5+ years	3	6	2.0	0.789	(0.55,7.22)
Special Products Manufacture (19)					
Ever	31	84	1.7	4.766	(1.14,2.61)*
2+ years	16	38	1.7	2.886	(1.02,2.78)
5+ years	4	10	1.5	0.546	(0.60,3.89)

*95% confidence interval also does not include 1.

CHAPTER VI

CONCLUSIONS

Epidemiologic studies conducted in Great Britain have demonstrated an excess in lung cancer mortality for rubber industry employees, compared to the general population of that country. In contrast, recent investigations of the mortality experience of rubber workers in the United States have not documented an excess in deaths attributed to lung cancer. A recent retrospective cohort study of 8,418 U.S. white male hourly rubber workers (83) reported a Standard Mortality Ratio of 80 for malignant neoplasms of the respiratory system for the years 1964 through 1973, indicating that the lung cancer mortality for these workers was lower than expected. The case-control study described in the present report was based on a lung cancer case series and control group selected from among deaths that occurred in this population of rubber workers and was carried out in order to determine whether history of employment in specific work areas in the rubber industry is associated with elevated risk for lung cancer mortality. The existence of such high risk work areas could not have been detected in the earlier retrospective cohort analysis, since detailed employment experience was not examined, and may have been obscured in a previous study (84) that focused on the work area in which subjects spent their longest amount of time and did not consider work area-specific employment of relatively shorter duration.

Several previous epidemiologic studies that addressed the possibility that elevated risk for lung cancer is confined to certain work areas have documented increased risks for lung cancer among workers engaged in the compounding and mixing of raw rubber stocks and in the curing of

green rubber products. Associations between employment in these two work areas and high risk for lung cancer have been demonstrated in more than one study and, therefore, were of particular interest in the present investigation. However, it was also felt that the possibility of the presence of additional high risk work areas should be explored in the current study.

The results of the present investigation do not support the findings of previous studies with respect to the compounding and mixing and curing work areas. Estimates of relative risk for these two work areas are uniformly close to one, indicating an absence of association between risk for lung cancer and history of employment in Compounding and Mixing and Curing, as defined in the present study. Cases employed for at least 1 month in Compounding and Mixing spent, on the average, a shorter period of time in this OTG than controls; among cases and controls employed for at least 1 month in Curing, cases worked only 2 years longer than did controls, on the average. Possible reasons for this apparent lack of association were advanced in Chapter V. It should be emphasized that the study design used for the present investigation may have resulted in conservative risk estimates. Thus, weak associations between lung cancer risk and employment in Compounding and Mixing and Curing may not have been detected.

An association between elevated risk for lung cancer and history of employment in Reclaim Operation is suggested by the results of this study. The observed association is strongest for workers who spent at least five years in this work area and who started working there 15 or more years prior to death. Further analyses will be conducted in order

to determine more precisely the time period, if any, during which maximum elevation in risk occurred. Definition of this time period would facilitate the identification of possible etiologic agents and, if consistent with the concept of a 15-35 year latent period, would constitute additional supportive evidence for the presence of an association between employment in Reclaim Operation and elevated risk for lung cancer. The presence of comparatively high levels of particulates and fumes from heated rubber suggests that the observed association may be biologically plausible. Further work by industrial hygienists is necessary in order to fully characterize the nature and extent of possible etiologic agents present in the Reclaim Operation work area.

The results of the present investigation suggest that there may be weak associations between history of employment in work areas designated as Chemicals (OTG 15), Pliofilm (OTG 16), and Special Products Manufacture (OTG 19). Little information is currently available with regard to agents, if any, that may have had an impact on the development of lung cancer among subjects who were employed in these work areas, and further work is needed to identify specific respiratory system hazards, if any, in these work areas.

The validity of the findings of this study depends to a large extent on the correctness of the assumption that other lung cancer risk factors not controlled for by the matching procedure employed in the study design did not vary according to work area in the population of rubber workers studied. Risk factors other than OTG-specific employment, that were not considered include urban residence, previous employment in industries involving exposure to respiratory carcinogens, and, most

important, cigarette smoking habits. The presence, extent, and direction of any bias due to lack of control for these potential confounders in the present study is unknown. It is not possible to refute the possibility that the positive associations detected in this study may have been the result of the differential, concomitant exposures of subjects employed in the putative high risk OTG's to non-occupational respiratory system carcinogens, such as those present in cigarette smoke. Therefore, the results of the present study should not be regarded as conclusive.

This study has not identified a strong association between history of employment in any one work area and substantial elevation in lung cancer risk. Furthermore, the facts that the mean ages at death for lung cancer cases and controls were nearly equal and that cases and controls tended to have worked for the same number of years suggest that no potent lung carcinogen was present in the occupational environment of the population of rubber workers studied.

It should be noted that the findings of the current investigation apply only to employees of the rubber plant under study. Because of the possibility of inter-plant variations with respect to the qualitative and quantitative nature of potential exposures in the various work areas considered and differences in industrial hygiene practices and environmental control measures, no statement regarding the work area-specific lung cancer risk among workers at other rubber plants can be made. Furthermore, since short-term workers may not have been included in the present investigation, no inferences regarding their risk for lung cancer should be drawn from results presented in this report.

The present study was conducted largely in the spirit of hypothesis generation rather than hypothesis testing. The purpose of the investigation was to identify high risk OTG's at the rubber plant under study. For this reason, the tests of statistical significance reported in this paper may be inappropriate. Furthermore, a large number of such tests were conducted, and chance elevations in test results may have occurred.

As previously noted, the OTG's considered in this study consisted of job groupings, based on similarities in process, product and location within the plant. No attempts were made to define specific jobs or exposures conferring the elevated lung cancer risks observed for certain OTG's. The nature and extent of environmental exposure hazards present in the jobs comprising these potentially high-risk OTG's require elucidation through further epidemiologic and environmental research efforts.

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Number		Nu
001	Batch Preparation-Tires	0
002	Batch Preparation-Tubes, Flaps, & Bladders	0
003	Pigment Blending	0
004	Cement Mixing	0
005	Cutting & Milling-Tires	0
006	Cutting & Milling-Tubes	0
007	Service-Batch Preparation-Tires	0
008	Service-Batch Preparation-Tubes	0
009	Milling-Treads	0
010	Milling-Plystock	0
011	Milling-Flaps & Bladders	0
012	Milling-Tubes	0
013	Milling-Miscellaneous	0
014	Calender Operation	0
015	Calender Tending	0
016	Roll Changing-incl. Trucking & Service	0
017	Plystock Handling-incl. Band Building	0
018	Liner Service (reroll, mend, clean)	0
019	Tuber Operation-Treads	0
020	Tuber Operation-Tubes	0
021	Tuber Operation-Flaps & Bladders	0
022	Tuber Service-Tubes	0
023	Tuber Service-Flaps & Bladders	0
024	Tuber Service-Tread Tuber (incl. booking & slitting)	0
025	Cementing-Treads	0
026	Bead Building	0
027	Tire Building	0
028	Service-Tire & Bead Building	0
029	Inspection, Repair, & Sort Green Tires (incl. trucking	0
030	Paint & Line-Green Tires	0
031	Valve Preparation	0
032	Tube & Flap Building	0
033	Curing-Tires	0
034	Curing-Tubes	0
035	Curing-Flaps (black)	0
036	Curing-Flaps (white)	0
037	Curing-Bladders	0
038	Curing-Valves	0
039	Mold Cleaning & Repair	0
040	Finishing & Inspecting-Tires	0
041	Repairing Tires	0
042	Finishing & Repairing-Tubes & Airbags	0
043	Finishing & Repairing-Flaps, Bladders, & Sleeves	0
044	Maintenance-Painting	0
045	Maintenance-Millwright	0
046	Maintenance-Electrical	0
047	Maintenance-Sheet Metal	0
048	Maintenance-Welding	0
049	Mechanic	0
050	Carpentry	1

Number	
051	Machinist
052	Maintenance-Misc. (pipefitters, cement finisher, etc.)
053	Power Plant
054	Quality Control Testing
055	Trucking (genl.)
056	Clerical
057	Janitor
058	Shipping & Receiving
059	Other Rubber Worker (tires & tubes)
060	Mill Mixing
061	Prep.-Reclaim
062	Devulcanizing-Reclaim
063	Milling-Reclaim (refining)
064	Service-Reclaim
065	Service-BB-Misc.
066	Cpd. & Mix-Chem. Prod.
067	Reaction Opr.-Chem. Prod.
068	Finishing (dry, bag)-Chem. Prod.
069	Ship. & Rec.-Chem. Prod.
070	Manufacture Foam Prod.
071	Rocket Liner Mfg.
072	Urethane
073	Vinyl Prod. Mfg.
074	Resin Prod. Mfg. (chemigum, pliolite, dispersite) 345A split
075	Pliofilm Mixing
076	Pliofilm Fabrication
077	Pliofilm Finishing
078	Batch Prep.-Ind. Prod.
079	Prep.-Ind. Prod.
080	Curing-Ind. Prod.
081	Finish & Inspect-Ind. Prod.
082	Other Rubber Worker-(non-tire & tube)
083	Batch Prep.-Hose & Belt
084	Fabrication-Hose & Belt
085	Curing-Hose & Belt
086	Finish & Inspect-Hose & Belt
087	Special Rubber Prod. Development (381A & 357A)
088	Other Worker (non-rubber-such as police, cafeteria, etc.
089	Batch Prep.-Synthetic Latex
090	Preparation & Reaction-Synthetic Latex
091	Finishing & Packing-Synthetic Latex
092	Rim Plant-Metal Treatment
093	Rim Plant-Forming & Machining
094	Rim Plant-Welding
095	Rim Plant-Finishing & Inspecting
096	Plastics-Production & Manufacture
097	Fuel Cell
098	Aerospace
099	Metal Preparation-(mostly degreasing operations)
100	Mechanical Building

Number	
101	Salary
102	Unknown
103	Inactive File
104	Retired
105	Sick Suspense
106	Layoff
107	Active
108	Dead
109	Leave of Absence
110	Misc. Absence
111	Anode Process (Coagulation dip)
112	Rubber Preparation
113	Retread
114	Adhesives
115	Exit From Work for Other Reasons
116	Disability Retirement
117	Absence for Military Service
118	Tube Building & Curing
119	Footwear

Appendix A-2

OT - OTG Dictionary

Occupational Title Group	Component OT's
1. Compounding and Mixing	001, 002, 003, 004, 005, 006, 007, 008, 060, 065, 078, 083
2. Milling	009, 010, 011, 012, 013, 079, 084
3. Extrusion	019, 021, 023, 024, 025
4. Calendering	014, 015, 016
5. Stock Preparation	017, 018
6. Tubes	020, 022, 031, 032, 034, 042
7. Product Fabrication	026, 027, 028
8. Curing Preparation	029, 030
9. Curing	033, 035, 036, 037, 038, 080, 085
10. Finishing, Inspection & Repair	040, 041, 043, 081, 086
11. Maintenance	039, 044, 045, 046, 047, 048, 049, 050, 051, 052
12. General Service	053, 054, 055, 056, 057, 059, 082, 088
13. Shipping & Receiving	058
14. Reclaim Operation	061, 062, 063, 064
15. Chemicals	066, 067, 068, 069, 070, 072, 073, 074, 0
16. Pliofilm Manufacture	075, 076, 077
17. Synthetic Latex Manufacture	089, 090, 091
18. Metal Products	092, 093, 094, 095, 099, 100
19. Special Products Manufacture	071, 087, 097, 098
20. Miscellaneous	111, 112, 113, 114, 118, 119
21. Exit	101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 115, 116, 117

Appendix A-3

SUMMARY DESCRIPTION OF OCCUPATIONAL TITLE GROUPS

FOR THE LUNG CANCER CASE-CONTROL STUDY

1. Compounding & Mixing

Natural and synthetic rubbers, accelerators, antioxidants, fillers, etc. are weighed and then mixed in banburies for the preparation of various stocks in making tires, tubes, flaps and bladders. Service personnel truck bulk materials and blended pigments to banbury operators for dispensing into the banbury. Cements for use throughout the plant are mixed in a separate area. Cements are solvents made of petroleum derivatives such as paraffin hydrocarbons (e.g. hexane, heptane, octane), aromatic hydrocarbons (e.g. toluene, xylene), chlorinated hydrocarbon (e.g. trichloroethylene), ketones (e.g. methyl ethyl ketone). Environmental exposure to particulates (e.g. carbon black, accelerators, antioxidants, talc) is higher than other areas of the plant. Exposure to solvents is expected where cements are prepared. In the Cutting and Milling OT's (OT's 005 and 006), various batches from banburies are milled into long sheets, dipped in talc solution, dried and stored. Particulate exposures may be similar in regard to certain ingredients to those in other OT's included in this OTG, with the possible additional exposure to rubber fumes and reaction products from the hot uncured rubber stock.

2. Milling

Rubber stocks are processed further under heat and pressure (on a mill) for softness, and a plastic state. Reaction products from the hot uncured rubber stock are the main contributors for environmental exposure. For OT's 079 and 084, there are exposures to particulates (e.g. talc) and solvents.

3. Extrusion

Rubber goes through a tuber (die) and is extruded as tread rubber. Tread rubber is then slit and cemented. Environmental exposures include reaction products and cement vapors.

4. Calendering

The rubber from the mill is rolled through the calenders into sheets (usually covering a fabric). The calendar stock is then cut and spliced for further use. Also included in this group is roll changing (changing rolls and trucking rolls to storage, etc.). There is potential exposure to reaction products from the heated stock.

5. Stock Preparation

Splicing of material for making tire plystock and bands and rerolling

fabric (liners) after the plystock is used is the primary operation in this group. Also cleaning and mending of liners when necessary. There is potential exposure to reaction products and some solvents.

6. Tubes

This involves the extrusion of tube, flap, and bladder rubber, the fabrication of tubes, flaps, and valves, and the curing and finishing and repairing of tubes. Environmental exposures are to talc, solvents (in valve preparation, OT 031), reaction products and fumes (in tube curing, OT 034).

7. Product Fabrication (Tires & Beads)

This involves all processes with building tires and beads and all processes in which tire and bead builders are serviced (trucking materials to builders). Exposures are to solvents and uncured rubber stock.

8. Curing Preparation

This process includes inspection of uncured tires for defects and repairing and spraying materials onto uncured tires to prevent sticking in the curing mold. Solvents and mold release agents are possible agents for environmental exposures.

9. Curing

The uncured products (tires, flaps, bladders, and valves) are cured under heat and pressure. Environmental exposures are to reaction products and fumes.

10. Finishing & Inspection & Repair

Trimming, balancing, labelling, buffing, repairing, force grinding, and classifying cured products are the major operations. Environmental exposures are mostly in buffing and repairing (solvents, and rubber dust).

11. Maintenance

Mold cleaning, trucking, mechanics, pipefitting, electrical work, welding, painting, carpentry, etc., are jobs throughout the plant. Varied exposures as a particular job may indicate.

12. General Service

All operations associated with power plant, quality control, trucking, janitors, clerical, etc. This is a miscellaneous group with a variety of different jobs and exposures.

13. Shipping & Receiving

All activities associated with receiving and unloading of raw materials and packing and loading finished products for shipping are included in this

category. Any exposures in receiving would generally be sporadic due to occasional leaks. There is little exposure in shipping.

14. Reclaim Operation

Scrap vulcanized rubber products are shredded for separation and sizing before the rubber is "devulcanized". By the application of heat and chemicals, the rubber compound is restored to its original plastic state by milling. Exposures are to particulates and fibers from shredding scrap rubber, chemicals and oils in devulcanizing areas and rubber fumes from milling.

15. Chemical Products

Bulk chemicals are brought into the plant and stored in tank areas. Chemical products are produced in reaction tanks generally in a closed process. The chemical products are finally put through a drying procedure and bagged. They are now ready for plant use or for shipping. Exposures are to chemical solvents and chemical particulates.

16. Pliofilm Manufacture

Natural rubber is masticated and mixed with other compounds in a banbury. The stock is next transferred to mixing tanks where solvents are added. The rubber mix is pumped to reactor vessels neutralizing tanks and filtered prior to spreading. The mixture is spread to desired thickness, dried and rolled as a finished product. Environmental exposures are mainly to solvents.

17. Synthetic Latex Manufacture

This is essentially a chemical plant making elastomers that approximate one or more of the properties of natural rubber. SBR (Styrene-butadiene) is the most important synthetic rubber. Others include neoprene, nitrile, ethylene-propylenediene, etc. Exposures are to the gases, liquids and vapors that are ingredients for the particular synthetic rubber being made and the dried product.

18. Metal Products

Raw steel is cleaned in a pickling tank prior to being shaped (by bending) and welded. Finished metal products are lastly inspected, repaired when necessary and spray painted. Exposures are to welding fumes and acid and solvent vapors.

19. Special Products Manufacture

These products are metal and rubber stock, to varying degrees, and include rocket liner manufacture, special rubber product development, fuel cell, and aerospace products. There are various exposures as a particular job may indicate.

20. Miscellaneous

This is a miscellaneous group for workers involved in a variety of jobs, not otherwise classified. Environmental exposures vary.

21. Exit

This is a group constructed for exits from plants for various reasons.

Appendix B

Additional Formulae Used in Analyses for the Rubber Worker Lung Cancer Case-Control Study

1. Paired sample t-test

$H_0: \bar{D} = 0$ $\quad$ $\bar{D}$ = the mean difference, $(\frac{\Sigma d}{n})$, where d is the difference between the value of a given variable for a case and the average value among his respective controls, and n is the number of matched groups.

$$t_{n-1} = \frac{\bar{D}}{\sqrt{s_d^2/n}},$$ Where the sample variance of the difference, s_d^2, $= \frac{\Sigma d^2 - \frac{(\Sigma d)^2}{n}}{n-1}$

Reference: 108

2. Two sample t-test

$H_0: \bar{x}_1 - \bar{x}_2 = 0$ $\quad$ $\bar{x}_1$ = mean of a given variable for cases;
$\bar{x}_2$ = mean of a given variable for controls.

$$t_{n_1+n_2-2} = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{(n_1-1)s_1^2+(n_2-1)s_2^2}{n_1+n_2-2}}\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}}$$

where s_1^2 and s_2^2 are the sample variances for cases and controls, respectively, for a given variable, and n_1 and n_2 are sample sizes for cases and controls, respectively.

Reference: 108

Appendix B, cont.

3. Chi-square test of association for m by 2 tables.

$$X^2_{m-1 \text{ d.f.}} = \sum_{i=1}^{2m} \frac{(O_i - E_i)^2}{E_i} \quad ,$$

Where O_i = observed cell frequency,
E_i = expected cell frequency,
m = number of rows.

Reference: 107

4. Chi-square test of association for the crude odds ratio.

$$X^2_{1 \text{ d.f.}} = \frac{N(ad - bc)^2}{n_1 n_0 m_1 m_0}$$

(see Figure 2, page 84, for explanation of notation.)

$X^2_{0.10} = 2.71$, $X^2_{0.05} = 3.84$, $X^2_{0.01} = 6.63$

Reference: 104

5. Chi-square test of association for the matched sample odds ratio, for variable ratio matched data.

$$X^2 = \left\{ \sum_{R=1}^{4} (f_{1\cdot} - f_{1R}) - \sum_{R=1}^{4} \left[\sum_{m=1}^{4} N_m m(1+R) \right] \right\}^2 \Big/ \sum_{R=1}^{4} \left[\sum_{m=1}^{4} N_m m(1+R-m)/(1+R)^2 \right],$$

where R is the matching ratio; m is the total number of exposed subjects in a given group; the N_m = the number of matched groups in which a total of m subjects is exposed, and $f_{1\cdot}$ and f_{1R} are defined as in Figure 3, page 86.
For example, if R=4, the N_m are defined as follows:

$$N_1 = f_{10} + f_{01}$$

$$N_2 = f_{11} + f_{02}$$

$$N_3 = f_{12} + f_{03}$$

$$N_4 = f_{13} + f_{04}$$

Reference: 104

6. Computation of a test-based confidence interval for odds ratio estimates.

Confidence interval (CI) = EXP $(\ln \widehat{OR})(1 \pm \frac{Z}{\sqrt{X}})$,

where $(\ln \widehat{OR})$ is the natural log of the point estimate of the odds ratio;

Z is a percentage point of the normal distribution (Z=1.96 for a 95% CI; Z=1.645 for a 90% CI);

and X is the Mantel-Haenszel chi.

Reference: 102.