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STOMACH CANCER AMONG RUBBER WORKERS
A CASE-CONTROL STUDY

Occupational Health Studies Group
School of Public Health
University of North Carolina
Chapel Hill, N.C.

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STOMACH CANCER AMONG RUBBER WORKERS
A CASE-CONTROL STUDY

by

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A Report for the National Cancer Institute
Public Health Service, Department of
Health, Education and Welfare

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I.C.-2

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Steven Bernard Blum. Stomach Cancer Among Rubber Workers: A Case-Control Study. Under the direction of Herman Tyroler, Dragana Andjelkovich, Carl Shy, Allan Smith and Michael Symons. The following report is an adaptation of the dissertation submitted to the faculty of the University of North Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology. In addition to the dissertation committee identified above, the following professionals contributed to this report: Earl Arp, John Gamble and Ted Williams.

SUMMARY

Mortality data collected for ten year cohorts (1964-1973) at two major tire manufacturing companies revealed an excess of deaths from stomach cancer, based on elevated point estimates of Standardized Mortality Ratios (SMRs) at these companies. The present analytic investigation was undertaken to examine possible associations between this excess and numerous occupational and non-occupational factors operating within the rubber industry.

This study utilized a matched case-control design, with two sets of two controls (for a total of four) matched with each case - the first set matched on age, race, and sex and the second matched on these factors, and on duration of employment as well. The former control group was used to test the hypothesis of a generalized effect of employment within the industry, which would be evidenced by a longer duration of employment among cases. The latter was used for examining for differences in the detailed work histories of cases and controls, after having ensured equal opportunity, by the matching constraints, for each

group to have worked anywhere within the industry and these analyses allowed us to draw conclusions concerning the risk of developing stomach cancer in relation to work within specific areas of the plant. In all, there were 102 cases of stomach cancer and 393 controls, with subjects from both sex and race groups included in the study.

A thorough literature review of the relationship between stomach cancer and pertinent occupational and non-occupational risk factors is presented in Chapters III - XII of the enclosed report, although these chapters need not be read for a thorough understanding of the findings.

After appropriate analyses, the two control groups were merged and examination of the data indicated that there was no statistically significant association between stomach cancer cases and numerous potential explanatory factors, such as nativity, education, age at hire, and total duration of employment within the industry.

This was followed by an analysis of the detailed work history of each subject, a history which contains a listing of each job held by the individual, as well as the dates during which these jobs were held. Using a system developed by the Occupational Health Studies Group (OHSG) at the University of North Carolina, the thousands of unique jobs within the industry have been condensed into a more manageable number of approximately 100 Occupational Titles (OTs) which share common production processes, and these OTs have, in turn, been further condensed into 20 standard Occupational Title Groups (OTGs) with even broader common features.

The work history analysis involved an examination of the histories of stomach cancer cases and their controls for different OT frequencies between the two groups, a finding which would indicate possibly different

exposures to known or suspect gastric carcinogens. Initial use of the standard OTGs did not reveal differences in possible exposure. After these analyses, a new job classification was constructed by expert OHSG environmental hygienists. This new classification grouped OTs thought to have potential for exposure to numerous known or suspect stomach carcinogens. Use of this system revealed that cases at one company had significantly different work histories from controls, and this difference involved a history of employment within OTs judged to have substantial exposure to detackifiers (anti-sticking agents). Further analysis indicated that this exposure, among the cases, lasted longer and occurred in an earlier calendar period than did the control group exposures. Because of the common use of talc as a detackifier, and the possible contamination of talc with asbestos, which is a suspect stomach carcinogen, the possibility exists that asbestos exposure may explain a substantial proportion of the observed stomach cancer excess.

INTRODUCTION

In 1970, the United Rubber Workers Union negotiated with the six major U. S. rubber companies for a comprehensive program of research into work-related health problems. The Occupational Health Studies Group (OHSO) at the University of North Carolina is conducting research within four of these companies. We have access to large, stable populations of industrial employees on whose health status we have already completed numerous studies, with many more still in progress. One of our most recent investigations has revealed a substantial excess of stomach cancer, based on Standardized Mortality Ratios (SMRs), among rubber workers, and we have accumulated evidence of the nature of the environmental agents within the industry which may be of etiologic importance. The OHSO has developed methods to analyze employee work histories, which is of prime importance in an industrial setting, enabling us to categorize work experience into distinct Occupational Titles (OTs), each of which shares common industrial processes. These OTs can be further condensed into broader categories called Occupational Title Groups (OTGs), which are helpful in initial analyses. While the OTs are not exactly similar in every company under study, the OHSO has developed a cross-classification system (Appendix I) which enables us to pool data across the companies and plants included in this investigation.

Retrospective cohort studies, which identified employee cohorts as of 1964, were initiated at one plant in each of two companies in Akron, at which time all active and retired male workers who were alive and between the ages of 40-84, were identified. The mortality experience of these cohorts was obtained from the companies' life and pension insurance departments, with additional data collected from various state departments of vital statistics when unavailable from company sources. At both companies A and B these data were collected through 1973, so we have ten-year cohort analyses at both plants. The U. S. general population was used as the referent (standard), from which appropriate age- and cause-specific rates were derived for the determination of "expected" numbers of cases, and the results are presented in Table 1.

However, since the completion of these analyses, additional gastric cancer deaths, beyond the termination years, have been recorded at both companies. Company B has also collected data on the mortality experience of a "running" cohort for the interval 1950-63. Table 2 presents the total pool of stomach cancer deaths available for this study. Despite this large number of potential inclusions, the cases actually included were part of the ten-year cohorts, with the addition of cases which occurred in 1974 and the first part of 1975.

The present study is based on 102 deaths from gastric cancer and examines, in case-control mode, the possible association between this disease and numerous non-occupational and occupational factors.

RATIONALE

Workers in the rubber industry are, or have been, exposed to a variety of chemical agents which are either clearly established carcinogens or are highly suspected of being so. Table 3 presents a partial list of chemical carcinogens believed to have been present in the working environment of the rubber industry. As can be seen, the three classes of chemical agents (benzpyrene, nitrosamines, and asbestos) most often correlated with the incidence of gastric malignancies are either used as such or formed during the industrial process. Table 2 presents the stomach cancer mortality data collected by the Occupational Health Studies Group (OHSOG) at the University of North Carolina prior to the initiation of the present study. In view of the high case fatality and the five-year survival rate of only 12 per cent, the use of mortality instead of incidence cases seemed justified for case identification. In those companies for which retrospective identification of populations at risk have been completed, standardized mortality ratios for males are presented. As is evident from Table 1, there is a 30-90 per cent higher mortality from stomach cancer for males, based on age-comparable U. S. national mortality data. It should be noted, however, that the indicated mortality excess in males is probably a conservative estimate, since the national data are compiled for all males, including those who are bed-ridden or disabled, within the specified age categories. The workers comprising the populations at risk within the rubber industry, however, are healthy enough to be actively employed,

and comparing their rates with national data would therefore probably result in an under-estimation, as witness the SMR of less than 100 for all causes (Column 1). This phenomenon is commonly called the "healthy worker effect" [1]. For this reason, Column 3 in Table 1, the adjusted-by-all-causes rate, gives a closer approximation of the true increase in mortality rate.

In view of the evidence of increased gastric cancer mortality among rubber workers, and the concomitant presence of known carcinogenic agents within the industrial environment, an epidemiologic study seemed appropriate. As mentioned earlier, the OHSG had already collected a substantial amount of data on employees of the rubber manufacturing plants, and the remainder of the pertinent information was available. A case-control epidemiologic study, by comparing the occupational histories of cases and controls, would be able to determine, most importantly, if the cases had some common work area or exposure not shared by the controls. If this were to be true, and we suspected it would be, then using as a population-at-risk only that sub-group of workers employed in high risk areas would be expected to yield standardized mortality rates far higher than the overall excess reported thus far, a finding which would be possible when the dilution effect is eliminated.

The case-control approach was chosen because it would allow us to immediately use the ascertainment of death collected for the period under study. In addition, other types of information, which were either immediately available or which could be feasibly collected, would allow us to examine other types of variables which are suspected of being

associated with the development of cancer. There are a number of advantages to this method. First, by analyzing both duration of employment and occupational histories we would be able to determine if length of employment within specific work areas was a good index of exposure to carcinogens and subsequent development of disease. Also, by gathering data on variables such as ethnicity, we would be able to control for these possible confounding factors. For instance, mortality rates from gastric cancer show significant geographic variation. Some Eastern European countries, such as Czechoslovakia and Poland, have mortality rates three to four times higher than those in the U. S. This may well have been a factor at some of the plants under study and has the potential to explain the entire observed excess within the industry.

The most provocative general finding has been the consistently elevated point estimates for the gastric cancer SMR in all companies and plants thus far examined, indicating that any responsible agent or agents may be used extensively throughout the entire industry and not limited to only a few facilities, and that the excess is probably not entirely explained by the presence of a single common confounder. The case-control design enables us to determine if cases are generally more associated with some specific aspect of the production process, both within individual plants and across the two companies, than their approximately chosen controls.

Table 1

Summary of Preliminary Stomach Cancer Mortality Data for Males
Employed in the Rubber Industry

Company	Race	Observed Number of Deaths	SMR		
			(1) All Causes	(2) Stomach Ca	(3) Adjusted by all causes rate $(3)=(2)\div(1)$
A	W & B	39	99	187	1.89
B	W	34	95	124	1.31

Table 2
Total Numbers of Stomach Cancer Deaths Ascertained from
Death Certificates, by Race-Sex Groups

Company	Race-Sex Group			
	WM	WF	BM	Total
A				
1. 1964-73 (a)	37	5	6	48
2. 1964-73 (b)	41	5	6	52
B				
1. 1964-73 (a)	36	4	2	42
2. 1964-73 (b)	41	5	2	48
3. 1950-63 (a)	24	1	2	27
4. 1950-63 (b)	28	1	2	31

a = UCD (Underlying Cause of Death) only

b = anywhere on death certificate, and not just UCD

Table 3

Partial List of Chemical Carcinogens
Believed to be Present Within the Rubber Industry

Nitrosamines

N-nitrosodiphenylamine
dinitrosobenzene
N-N-Dinitroso N,N-dimethylterephthalamine
1,2-dihydroquinoline

Polycyclic Aromatic Hydrocarbons

3,4 benzpyrene
chrysene
pyrene
1,2 benzpyrene
1,12 benzperylene
1,2 benzanthracene

Asbestos and Asbestos-Containing Talc

SIGNIFICANCE

While the rate of stomach cancer mortality in the United States has been steadily declining during the last four decades, rubber workers are experiencing a significantly elevated risk compared with the general population. In addition, the prognosis for stomach cancer is poor, with a median survival time of less than five months and a five-year survival rate of only 12 per cent [2]. There exists rather convincing evidence from animal studies that certain environmental pollutants are capable of inducing gastric malignancies, and many of these agents are present in the occupational environment of the rubber industry. This investigation was the first analytic study concentrating specifically on the stomach cancer problem among American rubber workers.

The overall objective was to identify work areas or jobs in which fatal stomach cancer cases have clustered, and there already was some preliminary evidence of case-concentration within the industry. From the results of this study, we hoped to be able to make definitive statements concerning the specific areas involved, and we foresaw the possibility of following with detailed measurements of pollutant levels which would result either in their removal from the production process or in the development of protective devices for the workers. It was also possible that this study would implicate previously unsuspected carcinogens and thus contribute to the existing theory of carcinogenesis. In addition, serious consideration was also given to the possibility

that carcinogens which are present in the industrial environment of the rubber industry and associated with a higher incidence of gastric cancer may also be present in the ambient air, in smaller doses, and may therefore be affecting the general population. The design of this study would permit us to draw conclusions about the effect of length of exposure and age at first exposure on mortality from this disease.

Only about 10 per cent of stomach cancer diagnoses are made when the disease is in a localized stage, during which surgical treatment is most effective. The five-year survival rate for those diagnosed during the localized stage and treated surgically is 50 per cent, compared with 12 per cent for all gastric cancer patients [2]. The impact of identifying those specific aspects of the production process in which workers are at highest risk was thought to be considerable, since workers in these areas who had already been inadvertently exposed would be alerted to their increased risk. This could result in diagnoses being made at an earlier stage of the disease process, thereby significantly improving the prognosis. More importantly, if carcinogenic agents were identified in the industrial environment, they could be either removed or replaced, or workers could be provided with protective gear.

NATIONAL AND INTERNATIONAL RATES AND COMPARISONS

Stomach cancer incidence rates vary considerably both between and within countries, and estimates of these rates differ according to the calendar period for which they are computed. In addition, many researchers use mortality, rather than incidence, rates because the former are more easily and accurately compiled. Mortality rates are considered a valid reflection of incidence because of the very short median survival time and the low five-year survival rates [2].

Doll [3] (Tables 4-6) and Dunham and Bailar [4] (Table 7 and Figure 1) have compiled data illustrating the international variation in age-adjusted mortality and incidence rates. While there is some variation in these rates, depending on which of the two are used, the general ranking of countries remains quite constant. Specifically, high rates were found in the USSR, Chile, Japan, Iceland, Finland, Central Europe, and most of Latin America. Geographical areas with low rates include North America, Africa, and Southern and Southeast Asia. Dunham and Bailar have condensed these data into a map (Figure 1) which illustrates the geographic areas with low, intermediate, and high rates. They found the highest male rates, based on mortality, in Soviet Russia (112 per 100,000) and the lowest in Singapore (1.6 per 100,000). Doll found the highest male rates, based on mortality, in Japan (153.1 per 100,000) and the lowest in the United States (18.7 per 100,000).

TABLE 4

Cancer of the stomach: annual incidence rates per 100,000 persons 45-64 years old, standardized for age

Country	Rate per 100,000		Male rate per unit female rate
	M	F	
Japan, Miyagi.....	231.6	169.5	2.0
Iceland.....	147.6	47.2	3.1
Chile.....	135.9	48.8	2.4
Colombia, Cali.....	107.2	57.3	1.9
Yugoslavia, Slovenia.....	103.3	45.7	2.3
Finland.....	102.3	44.6	2.3
Hawaii, Japanese.....	84.8	47.7	1.8
England, Liverpool.....	69.2	27.5	2.5
" , Birmingham.....	63.2	23.7	2.7
Puerto Rico.....	61.7	21.2	2.9
W. Germany, Hamburg.....	61.6	27.0	2.3
Jamaica, Kingston.....	56.0	21.4	2.6
Norway.....	53.9	23.3	1.9
Denmark.....	53.1	24.5	2.2
Israel.....	49.5	26.8	1.9
Sweden.....	46.2	22.2	2.1
England, S.W.....	44.7	14.5	3.1
Canada.....	43.0	18.7	2.3
New Zealand.....	42.6	18.9	2.4
England, S. Metropolitan.....	41.9	15.4	2.7
Singapore, Chinese.....	32.7	10.0	4.0
Netherlands.....	37.2	15.6	2.4
Nigeria, Ibadan.....	29.7	14.7	2.0
United States, Connecticut.....	26.5	15.4	1.7
S. Africa, Johannesburg Bantu.....	26.4	24.4	1.1
Hawaii, Caucasian.....	25.8	24.7	1.0
United States, New York State.....	23.2	9.6	2.4
Uganda, Kyadondo.....	8.7	4.1	2.1
Mozambique, Lourenço Marques.....	6.8	3.6	1.9

from [3]

TABLE 5

Cancer of the stomach: annual mortality rates per 100,000 persons
45-64 years old, standardized for age

Country	Rate per 100,000		Male rate per unit female rate
	M	F	
Japan.....	153.1	78.3	2.0
Chile.....	144.8	81.6	1.8
S. Africa, Colored.....	100.0	47.2	2.1
Poland.....	95.7	41.3	2.3
Czechoslovakia.....	80.7	38.6	2.4
Hungary.....	85.9	37.8	2.3
Romania.....	84.1	42.0	2.0
Finland.....	79.8	37.7	2.1
Austria.....	74.6	38.5	2.0
Portugal.....	71.6	35.3	2.0
Italy.....	67.6	29.6	2.3
Venezuela.....	65.7	42.7	1.5
Puerto Rico.....	65.6	21.7	3.0
W. Germany.....	65.2	29.9	2.2
N. Ireland.....	58.0	25.3	2.3
Colombia.....	54.6	37.5	1.5
Scotland.....	54.3	26.3	2.1
Belgium.....	53.5	24.1	2.2
England and Wales.....	49.9	20.2	2.5
Yugoslavia.....	48.9	24.1	2.0
Ireland.....	48.8	29.9	1.6
Norway.....	47.3	24.8	1.9
Hong Kong.....	46.8	29.8	1.6
Netherlands.....	46.6	20.9	2.2
S. Africa, white.....	44.9	22.6	2.0
United States, nonwhite.....	44.4	19.6	2.3
Switzerland.....	43.2	20.8	2.1
France.....	41.9	17.0	2.5
Sweden.....	38.4	20.3	1.9
Denmark.....	38.0	18.3	2.1
Israel.....	35.2	21.3	1.7
Canada.....	32.9	15.0	2.2
New Zealand.....	32.0	12.8	2.5
Greece.....	31.2	20.5	1.5
Australia.....	28.9	10.8	2.7
United States, white.....	18.7	8.7	2.1

from [3]

TABLE 6

DISTRIBUTION OF GASTROINTESTINAL CANCER

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Cancer of the stomach: annual mortality rates per 100,000 persons 40-59 years old, standardized for age

Country		Rate per 100,000		Male rate per unit female rate
		M	F	
Russia	S.F.S.R.	128.5	66.2	1.9
Kirgiz	S.S.R.	116.8	49.2	2.4
Kazakh	"	110.8	52.3	2.1
Turkmenian	"	109.0	45.7	2.4
Belorussian	"	95.1	49.9	1.9
Tadzhik	"	81.6	37.5	2.2
Uzbek	"	81.3	39.5	2.1
Ukrainian	"	77.4	37.9	2.0
Estonian	"	75.3	35.6	2.1
Azerbaijani	"	66.3	40.5	1.6
Moldavian	"	63.3	18.3	3.5
Lithuanian	"	61.6	28.1	2.1
Latvian	"	54.9	30.9	1.8
Armenian	"	45.7	21.8	2.1
Bulgarian	"	42.3	27.1	1.6
Georgian	S.S.R.	35.5	23.4	1.5

from [3]

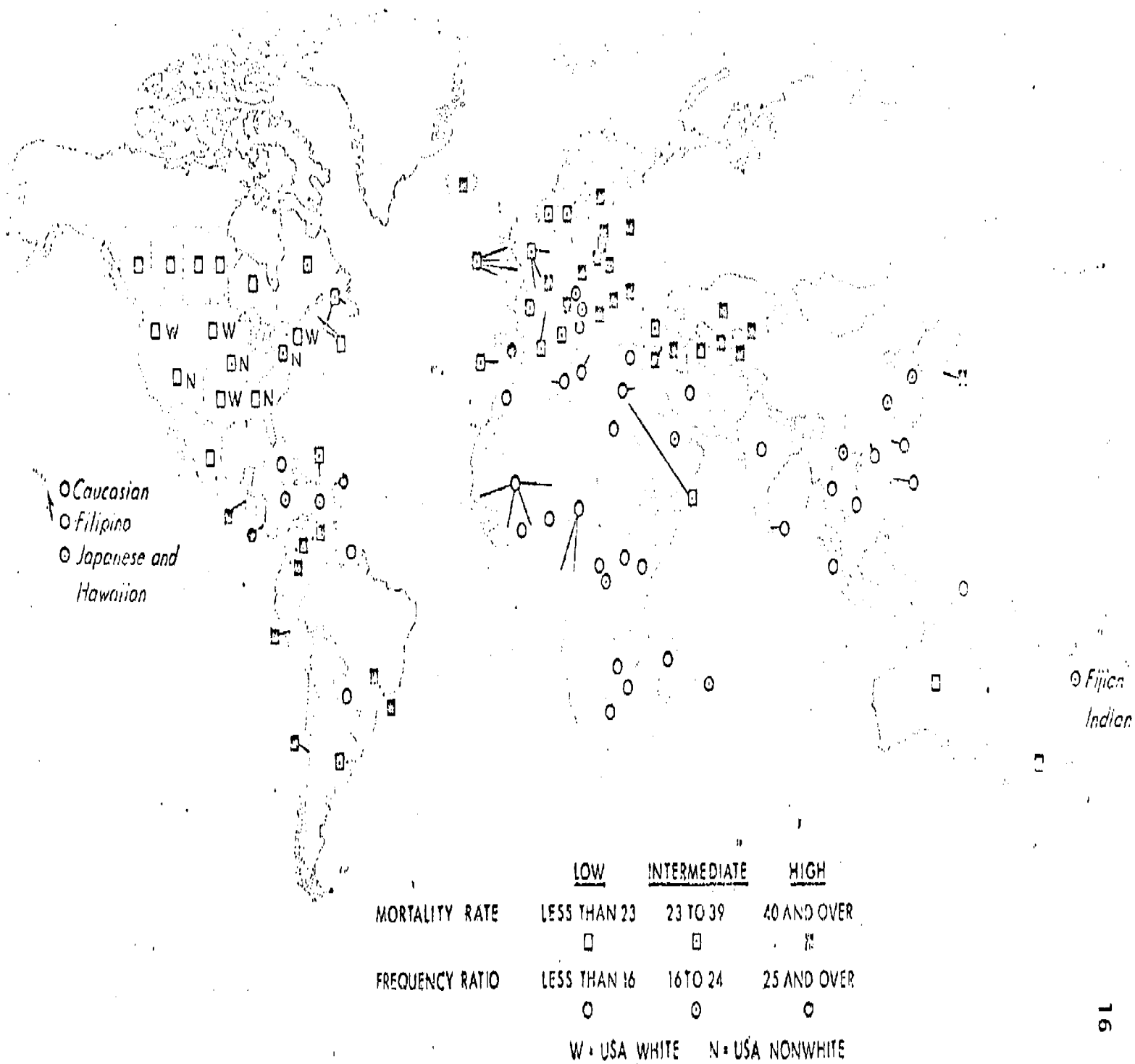
TABLE 7

FIGURE 5.—CANCER OF STOMACH, MALE (International List No. 151 (asterisks divide columns into low, intermediate, and high ranges)).

[illegible]

FIGURE 1

STOMACH, MALE /#151



from [4]

Among white males in the United States between 1950-67 [5] (Table 8) the lowest rates were found in South and North Carolina (9.76 and 9.90) and the highest rate occurred in North Dakota (20.77).

As is seen in Table 4-6, the sex ratio (male rate per unit female rate) is approximately 2.0, i.e., the rate of gastric cancer is twice as high among males compared with females in most countries. When the sex ratio, however, is correlated with the specific site of the cancer within the stomach, or with age, considerable variability becomes evident. Sterup and Mosbech [6] studied 1,983 consecutive cases of stomach cancer treated in Copenhagen hospitals during the period 1940-57, of which 1,212 diagnoses (61 per cent) were established histologically and 771 (39 per cent) were determined by other means (X-ray, during surgery, or at autopsy). Of these 1,983 cases, 43 per cent were in the pylorus, 36 per cent occurred in the corpus, 12 per cent were found invading the entire stomach, 5 per cent were confined to the cardia, and 4 per cent were in the fundus. They found that the sex ratios varied considerably by site. While the overall ratio was 1.7, the site-specific ratios were as follows: cardia - 4.0, fundus - 3.8, corpus - 1.8, pylorus - 1.5, and entire stomach - 1.2. MacDonald [7] studied 51 cases of adenocarcinoma of the cardia and compared their clinical features with those of 169 patients with cancer elsewhere in the stomach. He found the following sex ratios: cardia - 7, other - 2.3. Flamant, et al., [8] reviewed 298 surgical cases of gastric cancer and found a sex ratio of 3 for the fundus, cardia, and corpus, while the ratio for the pylorus was 1.4.

Griffith [9] found that the sex ratio, based on mortality rates, varies by age. He studied mortality rates in 24 countries for the six-

TABLE 8

MALIGNANT NEOPLASM OF STOMACH (ICD 151)

STATE	WHITE MALE		NONWHITE MALE		WHITE FEMALE		NONWHITE FEMALE	
	NUMBER	RATE	NUMBER	RATE	NUMBER	RATE	NUMBER	RATE
ALABAMA	2037	11.24	1422	19.88	1324	5.89	847	9.92
ARIZONA	1150	12.41	156	19.48	625	6.26	65	9.52
ARKANSAS	1764	11.35	727	19.67	1044	6.19	368	9.39
CALIFORNIA	17892	14.39	1974	24.00	11246	7.17	787	9.92
COLORADO	2085	13.91	90	22.66	1229	5.85	43	13.97
CONNECTICUT	4649	17.97	159	26.59	2471	8.70	50	7.11
DELAWARE	396	12.78	141	31.12	270	7.08	50	11.34
DISTRICT OF COLUMBIA	490	12.72	605	27.72	377	6.10	325	10.79
FLORIDA	4903	19.14	1303	22.35	2605	4.97	540	8.61
GEORGIA	2124	10.14	1570	21.12	1379	5.05	675	9.28
IDaho	860	14.04	19	21.38	422	6.89	16	22.51
ILLINOIS	14719	16.72	1757	26.39	9045	8.42	385	11.84
INDIANA	5230	12.76	463	24.17	3148	6.27	183	8.95
IOWA	4116	13.41	50	23.27	2510	6.60	25	9.99
KANSAS	2524	11.49	180	20.81	1400	5.56	72	7.78
KENTUCKY	3141	11.87	480	22.39	2132	6.91	231	9.76
LOUISIANA	2206	13.35	2380	31.92	1334	5.50	1151	13.53
MAINE	1702	16.94	3	10.20	1016	8.41	3	9.70
MARYLAND	2560	13.13	945	27.40	1825	7.14	432	11.31
MASSACHUSETTS	8794	17.66	217	24.42	6312	9.21	167	10.68
MICHIGAN	10848	17.87	1099	24.39	5743	8.34	495	10.52
MINNESOTA	6388	19.44	55	18.26	3517	9.23	24	8.04
MISSISSIPPI	1268	11.14	1595	22.24	876	5.46	968	12.27
MISSOURI	5444	12.45	817	24.77	3581	6.52	485	11.04
MONTANA	1029	15.36	33	21.38	514	8.80	13	10.93
NEBRASKA	2478	15.93	66	25.87	1404	7.66	26	9.79
NEVADA	333	14.44	26	18.05	132	6.48	13	11.78
NEW HAMPSHIRE	1053	16.60	5	46.18	686	8.32	2	20.04
NEW JERSEY	9725	19.92	816	25.15	6281	9.82	437	11.49
NEW MEXICO	971	17.56	55	14.05	559	9.66	26	8.54

from [5]

TABLE 8- [cont'd]

NEW YORK	28441	10.52	2475	27.43	18450	9.78	1400	12.59
NORTH CAROLINA	2487	9.90	1406	20.20	1655	5.33	729	9.07
NORTH DAKOTA	1306	20.77	12	10.57	714	11.70	7	9.91
OHIO	12250	15.10	1354	25.32	7307	7.42	506	10.62
OKLAHOMA	2027	12.74	372	18.35	1664	6.32	247	11.06
OREGON	2583	14.12	50	19.61	1342	6.62	25	10.34
PENNSYLVANIA	17603	17.15	1804	29.39	10795	8.62	733	10.66
RHODE ISLAND	1555	19.30	33	23.55	1053	9.97	15	9.51
SOUTH CAROLINA	1007	9.76	1136	23.46	601	5.89	584	11.52
SOUTH DAKOTA	1170	16.44	35	19.87	617	8.36	25	15.53
TENNESSEE	2807	10.91	979	20.49	1846	5.88	515	9.51
TEXAS	7955	12.01	2002	21.45	5124	6.42	1023	10.01
UTAH	817	13.43	46	36.51	499	7.08	15	15.83
VERMONT	556	13.67	1	9.90	345	6.53	1	9.20
VIRGINIA	2568	11.04	1465	24.60	1699	5.74	539	9.95
WASHINGTON	4199	15.35	191	20.22	2209	7.21	95	15.44
WEST VIRGINIA	2399	14.31	239	24.54	1345	7.37	95	10.60
WISCONSIN	7151	18.15	82	18.77	4300	9.51	45	10.60
WYOMING	306	13.82	8	15.88	177	6.60	5	12.03
UNITED STATES	222524	15.22	33606	24.03	137254	7.70	16725	10.69

from [5]

year period 1958-63. Overall, the mean ratio for all countries was approximately 1.0 for the youngest age group (25-29), rose steadily to a maximum of 2.23 at age 55-59, and then declined steadily to 1.46 at age 80-84. While these data are cross-sectional, Griffith cites evidence that the same trend can be seen in cohort studies as well and is therefore not a cohort phenomenon. This sex ratio pattern was remarkably similar in all 25 countries analyzed and was not seen in cancers in other parts of the gastrointestinal tract. Griffith attributes this sex ratio variability to calorie consumption and states that "the available data suggests that the sex ratio of total calorie consumption would fit the observed pattern after allowing for an appropriate latent interval."

SOCIOECONOMIC, OCCUPATIONAL, RELIGIOUS AND ASSOCIATED FACTORS

Numerous factors, some of which are of etiologic importance, influence gastric cancer incidence rates. Haenszel [10] conducted an exhaustive review of available data up to the year 1953 and looked at variations in age-standardized stomach cancer incidence and mortality in relation to demographic characteristics, socioeconomic status, urban-rural residence, geographic latitude, and nativity within the United States. He found a race ratio (nonwhite rate per unit white rate) of 1.33 for males and 1.28 for females, with this difference persisting in all regions of the country as well as in metropolitan and non-metropolitan areas. There were very small urban-rural differences, with the urban rates generally slightly higher. The greatest urban-rural differences were found in areas with large central cities: Los Angeles, New York, Chicago, and Cleveland. Haenszel points out, however, that this may be due to the fact that these cities have sizeable foreign-born groups. This small urban-rural disparity has been duplicated in England and Wales, Norway, and Finland. Levin and associates [11] also found very small urban-rural differences for both males and females in New York and in Connecticut and Iowa as well.

Stomach cancer mortality rates, Haenszel found, were higher in Northeast and Northcentral states compared with rates in the South, and the rates appeared to vary with latitude. This appears consistent with the observation that countries furthest north of the equator have

the highest rates, as is seen in Figure 1. Within the U. S., this pattern also seems to hold, based on Hoover's et al., [12] mapping of gastric cancer mortality by county. Based on three studies, Haenszel also concluded that the lower social classes exhibited the highest rates. Indeed, one study found this pattern in cases among married women classified by their husbands' occupation.

Gregor, et al., [13] reported on a 33-country ecological study where the investigators examined the mortality rates for all cancers against the rates for stomach and intestinal cancers and correlated these rates with the standard-of-living as measured by the intake of animal protein. They found that, while cancer in general was not correlated with protein intake, there was a strong negative correlation between protein intake and stomach cancer for both sexes. This again indicates that the higher social classes have the lowest rates. The authors, however, express the possibility that living standards may be related to other factors which influence the etiology or pathogenesis of cancer. Newell and Waggoner [14] determined the correlation between age-adjusted stomach cancer mortality rates and two indicators of socioeconomic status - per capita income and number of physicians per 100,000 population. They found negative coefficients of 0.87 and 0.77 for white males and females, respectively, for the former, and coefficients of 0.182 and 0.77 for the latter. They also correlated the death rates with the temperature index (mean annual temperature plus range) and found a very high negative correlation, a relationship which they suggest is not of etiologic importance and which may indicate a secondary association with social class. Davies and Griffith, [15] in their study of the relationship between soil and cancer to be

discussed later, also found that gastric cancer mortality rates were inversely correlated with social class.

Numerous investigators have examined, in depth, the association between social class and stomach cancer incidence. Cohart [16] studied all cases of carcinoma of the stomach in New Haven, Connecticut between the years 1935-49. Each case was assigned to one of twenty-four ecological (socioeconomic) districts based on residence. The districts were delineated according to a determination of the character of the dwellings in the area, along with other factors such as family income, occupation, dependency, delinquency, religion, race, and nativity. A total of 658 cases was collected during this period - 380 among males and 278 among females, although 22 were not available for study. The 24 districts were condensed into seven fairly homogeneous socioeconomic areas which ranged from rich to poor. Cohart found that the observed male rates were significantly lower than expected in the richest area and higher than expected in one of the middle and in the lower class area. When these seven areas were further reduced to three (well-to-do, middle class, and poor), the difference between observed and expected number of cases among females residing in the poor area became statistically significant, but significant differences for males disappeared, a finding which is in disagreement with the premise that social class and stomach cancer incidence are inversely related.

Graham, et al., [17] examined the records of all patients with cancer who were residents of Buffalo, New York and whose cases were reported to the Erie County Cancer Registry during the five year period 1948-52. Socioeconomic status was determined on the basis

of the median rental in the patients' census tract of residence according to the U. S. 1950 census. The 72 census tracts of Buffalo were divided into quartiles, with quartile I having the highest median rental. The investigators found that there was an increasing age-standardized stomach cancer incidence rate with decreasing socioeconomic status for both sexes. Among males, the age standardized incidence rates per 100,000 increased from 19.6-24.9-28.0-38.0 among those in quartile I to IV. Among females, the rates increased from 11.8-14.5-13.7-23.0. They also attempted to explain Cohart's inconsistent findings with the observation that New Haven had an unusually large proportion of Italian-Americans, most of whom were in the lower social classes, and that this ethnic group had extremely low rates of gastric cancer, although Italy is reported to have rather high stomach cancer mortality rates.

Seidman [18] examined the age-adjusted mortality rates among the non-Puerto Rican white population of New York City between 1949-51 for those aged 25-64. The rates were classified jointly by sex, religion, and socioeconomic status. The latter was defined according to the socioeconomic status of the Health Area of residence of the deceased. These Health Areas are combinations of contiguous census tracts of about 22,000 persons. Table 9 presents the results of the study. As is seen, there was, among males, an increasing mortality rate as social class decreased, but this pattern did not hold among females. When social class was cross-classified by religion, there were increasing rates among males within each religious group as social class decreased from high to low. Among females, however, this trend was inconsistent. Interestingly, there was not much difference

TABLE 9

DEATH RATE PER 100,000	MALE			GROUP	FEMALE			DEATH RATE PER 100,000
	NUMBER OF DEATHS	COMPARISON WITH WHITE MALES			NUMBER OF DEATHS	COMPARISON WITH WHITE FEMALES		
		PERCENT ABOVE	PERCENT BELOW			PERCENT ABOVE	PERCENT BELOW	
100,000	1955	1957	1959	1960	1955	1957	1959	1960
CANCER OF THE STOMACH (International List No. 151)								
23.4	14.03	1409.0		WHITE		7.60	760.0	12.9
19.1*	3.81	452.3		Whites by Socioeconomic Class		25.4	258.9	12.6
23.2	4.62	446.0		HIGH		24.0	261.2	11.8
27.7*	5.66	478.9		MIDDLE		27.5	249.9	14.2*
				LOW				
186**	1.37	172.7		HIGH J		11.3	50.5	15.0*
197**	2.44	300.0		HIGH NJ		15.1	178.3	10.9*
183**	1.24	157.3		HIGH C		9.3	109.1	11.0
21.2	1.20	132.7		HIGH P		5.8	59.2	10.8
21.6	1.24	134.6		MIDDLE J		7.1	71.6	12.8
23.3	3.33	332.5		MIDDLE NJ		16.6	169.6	11.3
23.5	1.89	184.8		MIDDLE C		11.5	121.6	12.2
24.2	1.49	144.0		MIDDLE P		5.4	58.0	10.2
36.2	16.3	145.9		LOW J		9.1	83.1	14.3
28.3*	4.03	303.2		LOW NJ		18.3	185.3	14.1
28.7*	2.47	195.1		LOW C		13.4	116.5	14.1
26.5	1.55	130.1		LOW P		4.9	50.0	12.8
21.9	12.4	453.2		Whites by Religious Group		27.7	249.6	14.5*
24.2	30.5	955.8		NJ		50.3	534.4	12.1*
24.2	5.0	541.0		C		34.2	347.2	12.7
24.9	42.5	414.8		P		15.1	187.2	11.1*
36.0*	13.6	89.7		NEGRO		9.8	98.4	21.6**
29.1	2.4	13.9		PUERTO RICAN		1.8	13.2	---
---	1.6	9.9		CHINESE, ETC.		2	0.9	---

FIG. 3. Cancer of the esophagus and of the stomach.

from [18]

between the rates of males and females of different religions, although one might expect the rates among Jews and Catholics, among whom there are a greater proportion of first and second generation immigrants, to be higher than the rate among Protestants. In fact, male Jews had the lowest rate of any religious group while females had the highest, although the range was rather small.

Newill [19] also studied cancer mortality among white residents of New York City. He investigated a total of 83,341 deaths, of which approximately 10 per cent (8,566) were ascribed to stomach cancer. Examination of religious affiliation was restricted to those aged 45 and over and rates were not age adjusted "on the assumption that variations in the religious distribution of the population by age is inconsequential after age 45", an assumption which must be seriously questioned. In addition, tests of significance were not presented. Newill found that for each sex separately, and for both sexes combined, Jews had the highest average annual death rate from stomach cancer, followed by Protestants and Catholics, although the differences were not very great. These conclusions, therefore, are in partial agreement with those reported by Seidman.

Buell, Dunn, and Breslow [20] analyzed 10,401 male cancer deaths in California among those aged 20-64 during the period 1949-51. Each death was assigned to one of five social class levels based on the reported occupation on the death certificate. The occupational-social class levels, based on "intuitive judgements," were developed by the National Office of Vital Statistics. The five categories, from highest to lowest are: professionals; intermediate; sales, clerical, and skilled; semiskilled; and unskilled. Farmers were excluded from the

classification. The investigators found a strongly increasing stomach cancer mortality rate from Social Class I to V, indicating a definite inverse relationship.

They also found nine occupations with an excess number of deaths, based on Standardized Mortality Ratios, significant at the 0.05 per cent level: Social Class III - bakers, masons, plumbers, toolmakers; Class IV - meatcutters and cooks; Class V - lumbermen, laborers, long-shoremen. Significant deficits were found in: Class I - accountants; Class II - teachers, managers, officials, proprietors in trade, in manufacturing and in "all other industries"; Class III - "other" clerical workers.

Kraus, Levin, and Gerhardt [21], in an excellent hospital-based case-control study, examined the relationship between occupational exposures and gastric cancer among males aged 25-74 admitted to Roswell Park Memorial Institute in Buffalo, N. Y., between November 1948 and September 1951. Occupational histories were obtained by personal interview and included all occupations in which the patient was ever employed. In addition, information about exposure to a specific list of physical and chemical agents were elicited from the patients. This was followed by the compilation, by a team of industrial chemists, of a probable list of exposures to physio-chemical agents based on the job descriptions reported. Information on a total of 56 stomach cancer cases was reported.

Four control groups were selected: 1. patients with digestive cancers other than stomach or esophagus; 2. non-digestive cancer patients; 3. non-tumor diagnoses of the digestive system other than esophagus or stomach; 4. other non-tumor diagnoses. A total of 667 controls was

selected in this manner. Each control group was matched with the case on age and population size of residence, apparently by group frequency matching, to eliminate the possibility that age or urbanicity would be responsible for any differences found. There were 18 broad occupational groups. Cases and controls were compared regarding the proportion who had ever worked in any of these groups and regarding the proportion who had ever been exposed to the specific physical and chemical agents. Duration and concentration of exposure were also examined.

Only one occupational group was significantly associated with stomach cancer - the metal-products occupation - in which there is exposure to iron dust. The investigators determined that 66 per cent of the cases and 43 per cent of the controls had ever worked in this industry, a difference which was highly statistically significant ($p < 0.002$). It should be noted that the proportion of both cases and controls ever employed in this industry seems exceptionally high, and perhaps the possibility of selective admission to Roswell Park should have been considered. At any rate, Kraus, et al., found that 12.5 per cent of the cases had been exposed to iron dust for 10 or more years against only 1 per cent of the controls. Subsequent to 10-year employment involving exposure to metals, 12.5 per cent of the cases had been exposed to grain dust for 5 or more years, usually as a farmer, compared with 1.5 per cent of the controls, although the authors suggest that the relationship between stomach cancer and farming life is probably dependent on some factor other than grain dust itself. Additionally, of all stomach cancer cases, 17.9 per cent were exposed to inorganic dust with free silica for 10 or more years against 7.8 per cent of the controls. These individuals were not included in the

iron dust and grain dust exposure groups. No significant differences between cases and controls were found when analyzed for smoking habits and marital status, but almost four times as many cases (23.2 per cent vs. 6.4 per cent) had been born in Poland ($p < 0.0001$), a finding which was independent of occupational factors. Sigurjonsson [22] examined the death certificates of all adult males between the ages 35-64 who died in Iceland during the period 1951-60. A total of 486 deaths due to gastric cancer were identified and proportionate mortality rates, which apparently were not standardized, were calculated for five socioeconomic classes into which all cases were categorized: I - farmers, II - labourers, III - seamen, IV - craftsmen, V - white collar workers. The proportion of all deaths due to stomach cancer decreased progressively (25 per cent - 19 per cent - 15.5 per cent - 9.9 per cent - 8.4 per cent), although it is difficult, it would seem, to infer that seamen, for example, belonged to a higher social class than farmers or laborers. The author attempts to correlate all differences in these classes to differences in dietary consumption of 3,4 benzopyrene, an attempt which may be of dubious value when based on proportionate mortality rates which, additionally, have not been standardized.

MIGRANT AND ETHNIC STUDIES

Lombard and Doering [23] in 1929, made the first attempt to analyze and compare cancer mortality rates for foreign and native-born. They studied cancer deaths in Massachusetts during the five-year period 1920-24, age-adjusted to the 1920 state population. Rates at numerous sites, including stomach, were calculated separately for male and female foreign-born, native-born of foreign parents, and native-born of native parents. Results for stomach cancer are presented in Table 10 and, as is seen, there is a definite decreasing trend from foreign-born to native-born of native parents in each sex. Surprisingly, females had higher rates in two of the three nativity categories, a finding which has not been duplicated and which must lead to a serious doubt about the accuracy of the data. The authors tried to relate the differences found in Massachusetts on a nativity basis to the differences found in England on an economic (social class) basis. Apparently, no attempt was made to standardize for socio-economic status, which seems feasible since age-standardization was employed. The attempt to explain the differences in this manner was supported by results of a survey which indicated that a greater proportion of foreign-born were poor when compared with the other two nativity groups (native-born of native and of foreign parents). When cancer death rates were analyzed by specific country of birth, it was found that Russians and Scandinavians had the highest rates among males while Teutons (Austria, Germany, Holland, Belgium) and Canadians

TABLE 10

Stomach Cancer Mortality Rates (per 100,000) in
Massachusetts, 1920-24, by Nativity

Nativity	Rates	
	Male	Female
Foreign born	35.5	30.5
Native born of foreign parents	20.8	22.4
Native born of native parents	11.8	14.3

from [23]

had the highest rates among females, a finding consistent with subsequent surveys. The authors conclude that foreign-born have much higher stomach cancer mortality rates than native born of native parents, and that stomach cancer rates are abnormally high among both males and females in all foreign-born groups. While there apparently were some shortcomings in collection and analysis of the data, Lombard and Doering should be credited with first realizing the importance of ethnicity in cancer incidence.

Choi [24] investigated the general ethnic distribution of gastrointestinal cancer mortality among the foreign-born in Manitoba during the years 1955-65, and presented SMRs based on the rates among native-born and all Manitobans from the 1961 census. A total of 1,198 gastric cancer deaths among foreign-born Manitobans was recorded during this period - 839 among males and 359 among females. For males, the average annual age-adjusted gastric cancer death rates among the foreign-born - 32.5/100,000 - were almost twice as high as among natives - 17.7/100,000. Immigrants from over twenty countries were included in this study and among males for every country, except the U. S., the SMRs were above 100, with the highest among foreign born from Scandinavia (SMR - 248), the USSR (SMR = 221) and Poland (SMR = 208).

Graham and associates. [25] studied all admissions, with regard to ethnicity, to Roswell Park Memorial Hospital between 1 January 1945 and 31 December 1956. Of the 35,701 admissions during this period, 18,677 were diagnosed as having some form of malignancy. A control group was chosen from admissions, during the same period, not associated with cancer and all findings are based on adjustment for variations in age, occupation, urban-rural residence, and tobacco use.

The investigators found that there were 21.4 per cent more foreign-born patients among the stomach cancer groups compared with the controls ($p < 0.0001$). The relative risk of gastric cancer among foreign-born compared with native-born was 2.5. When Poles were analyzed separately, they found that 22.4 per cent of the gastric cancer patients were of Polish origin, compared with 9.8 per cent of the controls ($p < 0.0001$); and Poles, overall, had a relative risk of 1.2 when compared against all other foreign-born. Adjustments were made for the four factors mentioned above because it was found that the various ethnic groups differed substantially in the distribution of these factors which are generally closely associated with cancer etiology.

Haenszel [26] examined all cancer deaths which occurred among foreign and native-born in 35 states in the U. S. during this single year 1950 and computed age-sex-site specific mortality rates for native white, total foreign white, and 12 major foreign-born groups (England, Iceland, Norway, Sweden, Germany, Australia, Czechoslovakia, Poland, USSR, Italy, Canada, and Mexico). Age adjustment was by the indirect method and SMRs are presented based on three separate referents - U. S. native whites, total whites, and referents derived from foreign countries. SMRs for gastric cancer, based on U. S. native whites, were statistically significantly elevated ($p < 0.01$) for total foreign-born whites and for foreign-born whites from each of the 12 countries used in the study, and the SMRs were elevated for both males and females. In fact, stomach cancer was the only site in which the SMRs were consistently elevated. Among males, they ranged from a low of 115 among Mexicans to a high of 171 among Czechs. Among females, the SMRs ranged from 130 among Canadians to 264 among

Czechs. Overall, the highest risks were found for migrants from Poland, Czechoslovakia, Norway, and the USSR.

Many investigators, both in this and other countries, have examined cancer incidence and mortality rates among Japanese and Polish migrants, especially in relation to stomach cancer, for which the two native countries have rates among the highest in the world. Smith [27] studied the mortality experience, for the years 1949-52, of Japanese residing in Hawaii and the continental U. S., based on information provided by the National Office of Vital Statistics. Both SMRs based on the indirect method of adjustment and rates derived from a direct adjustment were calculated but, since they were generally similar, only SMRs were presented based on two different referents - the white and non-white U. S. populations. When both male and female cancer rates among the Japanese were compared against the white and non-white U. S. populations, on which the SMRs were based, stomach cancer SMRs were significantly elevated ($p = 0.01$). Gastric cancer was the only one of approximately 15 sites studied for which the SMRs were significantly high in all four comparisons. For both males and females separately, the SMRs were approximately 300 when U. S. whites were used as a referent and 200 when compared with U. S. non-whites. These calculations were based on 395 male stomach cancer deaths and 125 female deaths.

Buell and Dunn [28] studied the Issei (first or immigrant generation Japanese) and Nisei (second generation) in California. Among the Issei, there were 16,377 males and 20,271 females, while the Nisei included 63,373 males and 59,424 females. Cancer deaths during the period 1949-62 were analyzed in two separate 7-year calendar periods, centered

around the years 1952 and 1959, to enable use of census data for 1950 and 1960. Generally, it was found that Issei males had gastric cancer death rates closer to male rates in Japan, where they are exceptionally high, than to the rate among white Californians. Male Nisei, on the other hand, had rates which were closer to those found among Californians.

SMRs were calculated separately for males aged 45-64 and for those 65 and over with the expected number based on the rates among California white males. Based on this referent, the SMR among those aged 45-64 for Japan was strikingly high at 840, while it was 380 for Issei and 280 for Nisei. In the 65 and over group, the SMR for Japan was 530 and 480 for the Issei (no data were available for the Nisei). The authors suggest that differences in diet or other environmental factors may account for some of these findings and rule out the possibility of bias due either to under- or over-diagnosis or false information about birth place.

Staszewski and Haenszel [29] studied age-and site-specific cancer mortality rates among the 860,000 Polish-born in the U. S., using Haenszel's technique described earlier. Rates among these migrants were compared with rates among U. S. native whites and with native Poles. The results indicated that gastric cancer mortality rates for both male and female Polish migrants were quite close to the rates in Poland among those aged 35-75. The authors state that "the persistence of characteristic dietary customs among ... ethnic groups in the United States assumes significance in this context."

Staszewski et al. [30] also studied the cancer mortality of Polish migrants to Australia, during the period 1962-66, and compared

the age-specific mortality rates of this group, for those aged 40 and over, with the rates in Poland and Australia for the period 1964-65. Among males, the migrant rates were intermediate between the high rates in Poland and the low rates in Australia for the entire age range 40 and over. Female rates were intermediate beginning at about age 50, but between 40-50 the rates were the same as those in Poland. Calculations were based on 59 male and 26 female deaths and three-quarters of the deaths occurred among those residing in Australia for a period of 7-18 years.

The intermediary position found here differs from a similar study by Staszewski and Haenszel, [29] cited above, where migrant rates were not intermediate, but were rather almost the same as Polish rates. Staszewski suggests that since the former study pertained to 1950 rates while this study involved 1962-66 rates, there is a "possibility that migrants' risks changed with time." He also suggests, as possible explanations for the different findings, the following: differences in length of residence in the host country, differences in the environment of the host country, and differences in migrants' backgrounds due to selection.

Monk and Warshauser [31] capitalized on a unique situation to investigate the relative importance of early environmental and constitutional factors on the incidence of stomach cancer. Generally when migrants are studied it is assumed that they have permanently left their country of birth and the finding that their mortality or incidence rates lie closer to the host than the adopted country can be explained on the basis of an early environmental factor, the effects of which linger despite the transition. There is in New York City a

large Puerto Rican population, however, which is unique because many of them return frequently to their native country and stay for unknown lengths of time. As a group, therefore, they are being continually re-exposed to the environmental factors prevalent in Puerto Rico, where mortality rates are higher than in New York City.

Deaths among Puerto Ricans in New York and in Puerto Rico, and among the white and non-white populations in New York City were examined during three periods: 1958-62, 1963-67, and 1968-71. Apparently, an indirect standardization was used, based on 1960 and 1970 census figures and on an intercensal estimate, and admission criteria were based on death certificate information. The results indicated that the age-adjusted mortality rates, among males, decreased during the three periods under study in each of the four population groups, while the same trend was seen among females, except for Puerto Rican born women, whose rates remained rather stable. In all three periods, also, the rates among Puerto Rican migrants to New York were lower than among Puerto Rican natives, and higher than among native whites in New York. These results parallel, to a degree, the findings of other migrant investigations, where the country of origin experiences rates higher than that of the host country. In this study, however, the rates among Puerto Rican migrants were closer to the rates in New York than to those in Puerto Rico, indicating that the occurrence of this disease is more responsive to recent, rather than early, environmental exposures, despite the fact that Puerto Ricans tend to return to their homeland often for extended periods. Other possible explanations offered by the investigators for these unexpected findings include: differences in diagnostic procedures and treatment, differences in resistance to

dietary changes, selective migration of Puerto Ricans at lower risk of developing stomach cancer, and selective return of migrants to Puerto Rico before retirement or death. The best explanation according to the investigators, however, is the "recency of migration and the young age of Puerto Rican migrants," which seems to account rather incompletely for the fact that rates among migrants were closer to those among native whites in New York, rather than to rates in Puerto Rico.

Tulchinsky and Modan [32] studied the incidence of gastric cancer among Jews in Israel for specific ethnic groups between 1961-63, based on 1172 cases. Israel is an ideal country for studying rates among different nationalities because of its exceptionally heterogeneous ethnic composition. Cases were classified into those with definite and probable diagnoses. The former were dependent upon either a post-mortem examination or on evidence from operative procedures with a biopsy, while the latter were based on explorative surgery, x-rays, clinical signs and symptoms, or death certificate information. The overall mean annual incidence was 23.4/100,000 among males and 15.0/100,000 among females, while the sex ratio was 4:1 for those aged 35 or younger and 1.6:1 among those over 35 years of age.

The cases were then classified into one of three population groups: immigrants from Europe, Africa, and Asia. Analysis of the age-specific rates revealed that male European immigrants had higher rates in every age group except among those 75 and over. The overall incidence rates were indirectly adjusted to the 1961 Israel population and ratios of these standardized rates are presented, although they are not really mutually comparable. The adjusted rates among males indicated a distinct gradient: Europeans = 25.5, Africans = 20.8,

Asians = 12.4, native Israelis = 8.7. When these were further analyzed according to specific country of origin, immigrants from the following countries had the highest rates: Rumania, Germany, Austria, Morocco, and Bulgaria. All but Morocco are eastern European countries, and these results therefore agree with the findings of other investigators.

On the basis of these ethnic differences in gastric cancer incidence and mortality, and on other analyses not mentioned here, Terris and Hall [33] considered the hypothesis that the decline in mortality from stomach cancer in the U. S. may be at least partly attributable to the change in the population composition; specifically, the declining rates may be a result of a decreasing proportion of foreign born, among whom the rates are highest, within the U. S.

Accordingly, they examined the age-specific mortality rate trends among three population group - white native-born, white foreign-born, and Negroes - in residents of New York City for two triennial periods: 1949-51 and 1959-61. The age-specific mortality rates, among both sexes in each of the three population groups, declined during the decade under study, and the age-adjusted mortality rates revealed that males had considerably higher rates than females in each of the three groups, with Negroes experiencing the highest rates, followed by foreign-born and then native-born whites.

Based on the declining rates within each of the three population groups, and on other pertinent information, the authors conclude that the declining mortality rate within the U. S. can be attributed neither to a decrease in the proportion of foreign-born, nor to improvement in therapy, and probably not to improvement in diagnostic

accuracy. The decline, instead, is considered to be "real" and can probably be explained by a decreased exposure to some unknown environmental or dietary factor 20-30 years (the incubation period) prior to mortality or alternatively, by an increasing exposure to some protective factor.

In addition to these international migration studies, there is at least one intra-national study of migration from areas in the southern region of the U. S. to the state of Ohio. Mancuso, [34] in this study, reports that non-white migrants to the state from the South experienced stomach cancer rates which were approximately twice as high as expected (28 observed and 13.7 expected). Unfortunately, not enough discussion concerning the many selective factors involved in migration is presented, which leads to a less than convincing argument.

DIETARY FACTORS

Dietary factors are, perhaps, the most attractive explanation for the vast differences in international gastric cancer incidence and mortality rates and for differences between groups, with different attributes, within countries. After all, all people have the potential for exposure to presumed carcinogens in food, especially in view of numerous animal studies which have indicated that many food additives and preservatives are indeed carcinogenic, either in their primary form or after metabolic or bacterial conversion. Dietary factors are also tempting explanations for the results of migrant studies, which generally indicate that first generation migrants experience rates closer to their home rather than host country, while second and third generation offspring gradually approach the rates of the host country. It is reasonable to assume that the latter also gradually alter their diet as they are assimilated into the host country culture. The problems in assessing an accurate dietary history in retrospective studies, however, are overwhelming. If the latency period is assumed to be on the order of at least two or three decades, prior to which there must have been sustained exposure to the putative carcinogen, the investigator must precisely estimate the specific dietary components quantitatively and chronologically. Since this is rarely, if ever, possible, qualitative estimates are often accepted instead. While even the latter can generate leads and hypotheses, it is

difficult to accept these results as strong evidence for implicating a specific food or carcinogen as being of causative importance in the etiology of gastric cancer, despite statistical significance. These problems are compounded by the fact that investigators generally do not provide, in scientific papers, the questionnaire used in their studies, so that a comparison of results is often difficult and may, in fact, be meaningless.

Naturally, it would be ideal to conduct prospective studies to determine the relationship between dietary consumption and subsequent development of stomach and intestinal cancers, although opportunities for this type of study are, at best, infrequent. Perhaps this type of investigation could be incorporated into large intervention trials, such as the LIPID study being conducted by the Department of Biostatistics and Epidemiology at UNC, if participants were relatively young at entry and, if these individuals have a high compliance rate with the dietary demands for a long period of time subsequent to inclusion in the study. Despite these shortcomings of dietary investigations, findings cannot be ignored, although they should be interpreted with great caution.

Bjelke [35] has exhaustively reviewed the literature on case-control dietary studies and its relationship to gastrointestinal cancer, and he concluded that "findings indicating any association between diet and these cancers ... were few, equivocal, and sometimes conflicting." However, he found the evidence of a negative association between gastric cancer and intake of vegetables fairly strong. While a negative association between consumption of fruits and Vitamin C were found by two investigators, they explained these findings as

being either a consequence of the gastric condition or as a secondary association, with the primary relationship between socioeconomic status and gastric cancer. Nevertheless, no studies have indicated a higher intake of fruits or vegetables among stomach cancer patients compared with controls. Intake of highly salted foods was the only dietary factor which was convincingly positively associated with stomach cancer.

Bjelke also nicely summarizes the major methodologic problems encountered in case-control dietary studies.

"Most reports give little specific information about the actual dietary questions that were used and what time period they referred to, few details are given on the selection of cases, no mention is made of how they might correspond to all new cases occurring in a defined population, and information which might aid an assessment of how the source population for the controls might compare to the general population on pertinent variables is almost equally scarce."

It should be reiterated, however, that methodologic problems and inconsistencies notwithstanding, dietary hypotheses are still attractive and may yet explain variations in gastric cancer incidence in either a primary or secondary manner. As an example of the former, Shamberger et al. [36] suggest that the declining gastric cancer incidence in the U. S. may be partly attributable to dietary factors: the widespread consumption, beginning in 1920, of wheat cereals rich in antioxidants, and the increasing use of antioxidants as food preservatives which began in the last 1940's. Antioxidants act by terminating the propagation of chain reactions which accelerate the oxidation process, and Shamberger suggests that antioxidants applied near the site of carcinogenesis may prevent peroxidation and attachment of the carcinogen to DNA, which may be one of the rate limiting steps in carcinogenesis.

Some of the most common antioxidants are BHT (butylated hydroxytoluene) and BHA (butylated hydroxyanisole), as well as lecithin, selenium, and tocopherols. While gastric cancer rates have been declining steadily since 1930, the author points to the deflection in the curve in 1947, heralding an even more rapid decline. This, he implies, could be explained by the introduction of the antioxidants BHA and BHT as food preservatives.

In the spirit of an ecological comparison, Shamberger examined 14 male cancer sites in 17 paired cities, with the latter dichotomized into high and low selenium consumption areas, but the method of assignment of cities into high or low selenium areas is not discussed. He found that, for all gastrointestinal cancers, the high selenium areas had lower SMRs, although the choice of a standard was not identified.

Correa and associates [37] on the other hand, present a model for gastric cancer pathogenesis in which dietary composition plays a secondary role. They postulate that "intestinal type" gastric carcinoma results from mutations and cellular transformations which begin during the first decade of life but which are mediated by abrasive or irritant food substances, such as hard grains or salty foods, which permit the carcinogen to pass the mucous barrier of the stomach, if the synthesis of these substances is not initially by the presence of antioxidants.

OTHER RISK FACTORS

ABO Blood Groups

Stocks, [38] in a study of geographic variation in the incidence of stomach cancer, found that towns in England and Wales whose water supply was of moderate hardness had lower standardized mortality rates than towns whose water was soft or very hard. The former were mostly in southern, and the latter in northern, counties. Aird, et al., [39] however, felt that the true correlation may not be with water hardness but rather with genetic differences between northern and southern provinces, as reflected in the frequency of ABO blood groups. They drew cases of stomach cancer from "a number" of hospitals in England and Scotland whose diagnoses, in most instances, were based on histological evidence but, in "a few" cases the diagnosis was based on non-histologic findings. An unspecified number of controls was obtained either from "a cross-section of the patients from the hospital concerned" or from "local transfusion centers" which putatively represent the general population of the locale from which the patients were drawn. While they did not prove their original hypothesis, they found that blood group A was more frequent, and O less frequent, in patients suffering from stomach cancer compared with the blood group distribution, based on the control series, found in the general population of the same locality.

Buckwalter, et al. [40] conducted a case-control study with cases drawn from six hospitals. Individuals were included in the study

if both their blood type and a histological diagnosis of stomach cancer were available. Overall, they found an excess of type A among cases (52.1 per cent) which was significantly different from the proportion of type A among controls (47.6 per cent) who were selected from among "healthy" blood donors at either of two hospital blood banks. There was no apparent matching for sex and age, which admittedly may not be confounders with respect to blood type, nor was there any matching for ethnicity, which may be a confounder. There does, however, seem to have been an attempt to control for these factors in the analysis, although sufficient data are not presented.

Some investigators have broadened blood type analyses to include the site of the cancer within the stomach. Billington [41] attempted to demonstrate that carcinoma of the stomach is associated with differing ABO blood groups dependent upon the site of the cancer in relation to the three major types of gastric glands. He studied 483 cases of adenocarcinoma of the stomach, excluding those which occurred among immigrants, at the teaching hospitals affiliated with the University of Sydney during the period 1947-54. All diagnoses were confirmed microscopically and classified according to involvement of the three major types of gastric glands, based on the site of the lesion - cardiac, body, and prepyloric. He then, like Aird, [39] compared his results with the ABO blood type distribution of blood donors from the same geographic area.

His analysis indicated that there was no overall association between blood group A and carcinoma. When further analyzed by site, however, there was a significant association between type A and prepyloric and cardiac lesions, while the body and fundus were

significantly associated with blood group O. Billington attempts to explain Aird's findings of an association with type A by suggesting that Aird may have had a greater proportion of prepyloric and cardiac lesions in England, along a generally greater percentage of blood type A's, compared with Sydney which, from other evidence, may be true.

White and Eisenberg [42] reported similar findings. They examined 707 cases of gastric cancer and categorized them by blood type, site, sex, age, and place of residence. Sites were determined from hospital records, pathology and radiography reports, or from findings at surgery. They found that blood group A was commoner than O in the series as a whole, with the excess of A most marked among males with cancer in the pyloric region. These site specific analyses may help explain negative findings by other investigators, such as those of Crumb and Willets [43] who concluded, on the basis of 123 cases of gastric cancer, that there was no association with blood group A.

Tobacco and Alcohol

Flamant [44] and his group in France has examined the relation between smoking and alcohol use and the incidence of gastric cancer. One survey included 64,834 cancer cases recorded between 1943 and 1960 and the investigators found that, in general, the higher the correlation between a site and the use of alcohol and tobacco, the higher was the standardized sex ratio. In addition to this large survey, the study included a series of 298 surgical cases of gastric cancer selected with "great diagnostic accuracy", although the selection criteria are not offered. They found that the sex ratio for the fundus, cardia, and corpus was 3, while it was 1.4 for the

pylorus. The authors imply that since females smoke and are believed to drink more infrequently than males, a strong association between smoking or drinking and cancer will result in a higher sex ratio. This sex ratio would therefore provide evidence for an association. However, in another investigation conducted by this group, [45] the conclusions differ. The study was a retrospective analysis of 3,937 male cancer patients matched for age and interviewer with two controls - one healthy and the other ill but not cancerous. The authors found no differences between stomach cancer cases and controls in the proportion of smokers, total amount smoked, and in the proportion of cigarette smokers who inhaled the smoke.

Hammond, [46] however, did find some differences, based on a prospective study of over one million persons, of whom 422,000 males between 40-84 years of age were followed for approximately three years. This group included smokers and non-smokers and the investigators determined that the stomach cancer mortality ratio for smokers:non-smokers among males aged 40-69 and 70-89 was 1.39 and 1.38, respectively. For gastric ulcer, however, the corresponding mortality ratios were exceptionally high - 5.38 and 2.97, respectively. It would seem that the smoking ratios of peptic ulcer and gastric cancer cases should be similar if ulcer is a precursor, unless ulcer patients who smoke selectively experience a higher mortality rate than do non-smoking ulcer cases.

Wynder [47], as chairman of a gastrointestinal cancer conference in 1965, concluded that "there appears to be no association between tobacco and gastric cancer". Zacho, et al. [48, 49], in a series of papers, have attempted to refute this conclusion. One of their studies

did not include a control group of any kind, and while we are informed that the cases were drawn from admissions to the Finsen Institute in Copenhagen between 1948-69, no mention is made of the selection criteria or of the proportion of cases interviewed. In another study apparently drawn from the same hospital, there is an attempt to compare the proportion of cases who ever smoked with a survey of smoking habits conducted by the Danish National Health Service in 1952-54. The study was poorly designed and the comparisons are of dubious value since there was no standardization of information collection. Nevertheless, the investigators attempt to explain the sex ratio for gastric cancer, which they determined from their study, by the difference in tobacco consumption in the two sexes and conclude that "this would seem to be a weighty indication of the aetiological role of tobacco."

Stocks [50], using an ecological design which he seems to prefer, studied the age-adjusted mortality rates at different sites in 20 countries for the period 1905-65 and correlated these rates with average national consumption of four commodities: cigarettes, tea, coffee, and solid fuel. He found no statistically significant associations between stomach cancer rates and any of these commodities although significant associations were found in both sexes between solid fuel and tea consumption and rates of intestinal (excluding rectum) cancer. Stocks attempts to explain these findings by stating that only a limited proportion of people are susceptible to gastrointestinal cancers but the most likely target, in the presence of certain carcinogens, seems to be the intestine. There appears to be a conviction among some investigators, therefore, that there must be an association between smoking and stomach cancer, notwithstanding the equivocal results.

For alcohol consumption, also, there is no convincing evidence of any association. This was the conclusion reached by Bjelke [35] in his thorough review and also by the Flamant [44] group cited above. Graham et al. [51] reached similar conclusions from a retrospective dietary study of 168 male and 68 female gastric cancer patients at Roswell Memorial Institute. They matched cases on age, country of birth, and nationality with non-neoplastic gastrointestinal disease controls and found no relationship between gastric cancer and frequency of use of various alcoholic beverages. The possibility should be considered, however, that alcohol may be of etiologic importance in both cancerous and non-cancerous gastrointestinal diseases, in which case one would not expect any differences between the two groups.

Soil and Fertilizer

Davies and Wynne Griffith [52] studied cancer mortality in Anglesey County, England, during the years 1943-52 in relation to soil type near the home of the decedent, social class, and water supply. A total of 178 male cases of gastric cancer and 140 female cases were examined, and expected numbers were calculated on the assumption that the proportion of cancers at a specific site having a specific attribute (e.g., soil type) was the same as the proportion of all cancers with that attribute. Soils were classified according to two criteria: nature of the parent material and seasonal productivity as determined by moisture content and drainage. Water supply was categorized into two groups - public mains and other sources, including wells, springs, and stored rainwater.

For stomach cancer, highly statistically significant associations were found for soil, social class, and water supply. There was a

relative excess of deaths seen on B-soils (which show great biologic activity over a long season), among those of low social class, and among those whose water supply came from "other" sources. The general association between gastric cancer and soil remained intact even after adjustment for age, sex, water supply, and social class, although the association maintained statistical significance only among those 65 years of age and older.

Tromp and Diehl [53] studied the relationship between major regional soil types and mortality from stomach cancer in the Netherlands between 1946-52. A total of 14,072 deaths were studied in this manner and they found that, in almost every age group, those living near riverclay and ordinary sandy soils had averaged stomach cancer mortality rates below the national average, while those living near sea-clay, peat, and reclaimed peat soils had higher rates in every age group. While the authors were unable to explain the observed relationships they expressed the opinion that it was, at least to some degree, of etiologic importance, perhaps because of differences in trace element distributions within soils. Unfortunately, they make no mention of how their soil classification compared with that of Davies.

Stocks and Davies [54] examined the zinc and copper content of the soil in gardens of people who had just died of cancer (cases) and other diseases (controls). To qualify, the person must have lived in that house for at least 10 years, on the assumption of a latency period at least that long. They computed the logarithm of the zinc:copper ratio and found that the average log of the ratio was higher in the gardens of people who had just died from gastric cancer after 10 or more years of residence, compared against houses whose occupants had died of other

causes. Similar analyses of other cancer types showed no differences between cases and controls.

While the investigators did not postulate any possible carcinogenic mechanisms involving copper or zinc, they suggest that the zinc:copper ratio may be of importance and demonstrate that, while there is no statistical association between zinc and copper soil content separately with potatoes grown on it, there is a fairly strong correlation between the ratio in the soil and potatoes grown on that soil.

In a recent ecological study by Armijo and Coulson [55], there was an attempt to correlate the use of nitrogen fertilizers in Chile with the stomach cancer mortality rates in different provinces of that country, which ranks second in the world in mortality from stomach cancer. The investigators found that the three counties with the highest nitrogen fertilizer use during the period 1945-1972 had the highest age-adjusted gastric cancer mortality rates for the fifteen year period 1957-1971. These findings, the authors state, would agree with the demonstrated ability of certain bacteria to synthesize nitrosamines from secondary aromatic amines and nitrates within achlorhydric stomachs.

Liquid Parrafin

Boyd and Doll [56] determined the frequency of use of purgatives among 614 patients with gastrointestinal cancer and 1313 controls. Of the 614 cancer patients, 387 had cancers of the large bowel and 227 had stomach cancer. Half of the controls had lung cancer and the remaining half had non-gastrointestinal diseases other than cancer. Expected numbers of those who "never, occasionally, or often" used purgatives were based on the experience of the entire group - both cases and

controls. The overall difference between them in the use of purgatives, after adjustment for age and sex, was not statistically significant ($p > 0.1$). However, when use of specific types of purgatives was considered it was found, from an analysis of age and sex specific rates, that the proportion of cases who used liquid paraffin was approximately twice as high as the proportion of users of this type among controls. Analysis of the age and sex-adjusted expected and observed numbers of "often" users revealed that among all gastrointestinal cancer patients combined, and also among stomach and large bowel cases separately, the use of liquid paraffin was statistically significantly more frequent among cases compared with controls.

Liquid paraffin is a mixture of liquid hydrocarbons obtained from petroleum. While the purification process should remove most of the polycyclic compounds, the authors found that this did not always occur. They express the opinion, however, that liquid paraffin is probably not of direct etiologic importance, but may be associated with some other unknown etiologic factor.

Graham et al., [57] based on a case-control study of 188 male and 88 female cases of stomach cancer and 800 non-neoplastic, non-digestive disease controls, reported similar findings. In their group, cases were significantly more frequent users of cathartics, although the specific types of cathartics were not determined. These investigators caution that purgative use may be secondary to another relationship, such as chronic constipation, with this disease.

Betel Chewing

Schonland and Bradshaw [58] undertook an ecological study to determine the relation between upper alimentary tract cancers and betel chewing among South African Indians in Durban. Age-adjusted cancer incidence rates were calculated for Indians and English of both sexes, and they found that Indian females had a significantly greater incidence of upper alimentary cancers than did English females, while there was no differences between males. Among the former, the stomach cancer incidence was 30/100,000, while the latter group experienced an incidence of 12.4/100,000. The investigation further established that a far greater proportion of Indian women than men chew betel and that, among chewers, females chew more heavily than males. Specifically, 8.3 per cent of Indian males and 54.2 per cent of the females aged 20 and over are addicted to betel chewing. No attempt, however, was made to analyze the cases themselves for betel chewing characteristics.

ANTECEDENT CONDITIONS

A constellation of inter-related factors - peptic ulcer, gastric polyps, gastritis, achlorhydria, and pernicious anemia - have been implicated in the etiology and pathogenesis of gastric cancer, although the evidence for the involvement of these factors is equivocal and often in dispute.

Ulcers are only rarely, if ever, considered to be precancerous lesions, although some investigators feel that they may be foci of increased susceptibility, since the integrity of the gastric mucosa has been destroyed. However, it is difficult to distinguish an ulcerating primary carcinoma of the stomach from one developing secondarily in a peptic ulcer, which complicates the problem of determining antecedent-consequent relationships. Additionally, an existent ulcer may possibly be overgrown and concealed by a secondary carcinoma, thus masking the co-existence of both. Numerous investigators have histologically examined ulcer series for the presence of cancerous development. Elliot, et al. [59] examined 109 ulcers and found that 0.8 per cent in the greater curvature were malignant while 2.2 per cent of those in the prepyloric area were cancerous. Cohn, et al. [60] differentiated peptic ulcers by size and found that, of a total of 533 patients with ulcers, 28 per cent of the ulcers measuring less than 2.5 cm. in diameter were cancerous, while 37 per cent of those greater than 4 cm. were malignant.

Hirohata and Kuratsune [61] investigated the geographical relationship between mortality from gastric ulcer and carcinoma in Japan, where mortality rates from stomach cancer among males were the highest in the world in 1962-63, as were gastric ulcer mortality rates for both males and females. Based on results of pathological examinations by other investigators, the authors estimated the ulcer/cancer rate to be between 2.5 per cent and 39 per cent, and the relative risk of developing stomach cancer, among those with ulcers, has been estimated to be approximately five. The investigators were of the opinion that the geographical variation in the incidence of gastric ulcer and carcinoma should follow similar patterns if either of two hypotheses are true: the carcinoma develops from the ulcer or both conditions have similar etiologies.

Accordingly, indirectly age-adjusted rates were calculated for two triennial periods (1949-51 and 1959-61) separately for each sex and each prefecture in Japan. Correlation coefficients were then calculated for different combinations of calendar period, sex, and disease. There was essentially no correlation, in either sex, between mortality rates of stomach cancer and ulcer during the two periods under study, nor was there any significant correlation between the ulcer mortality rates during 1949-51 and the cancer mortality rates ten years later, on the assumption that a substantial amount of time would be necessary for the development of cancer from ulcer. The possibility that this latter comparison may be misleading because of the potentiality that those ulcer cases at high risk, for some reason, of developing cancer had already died, leaving only the low risk ulcer cases alive, was not discussed. The authors do admit that ulcer

mortality rates are not the best measure of incidence because the case-fatality rate is low and that selective migration and accuracy of diagnosis are potential problems, but they do not feel that their conclusion of no association between the two diseases would be challenged by these shortcomings.

Gastric adenomatous polyps are also considered by some to be direct precursors of cancer. Polyps are benign glandular neoplastic growths and cellular atypias are often, but not necessarily, present. Bera [62] presents histologic observations on a series of 106 gastric adenomatous polyps from 45 patients. Of these polyps, 13 per cent showed a definite transition, within the polyp, from benign to invasive cancer, while 65 per cent had some degree of cellular atypia. Berg concludes that adenomatous polyps may be precancerous lesions and that they are reflections of generalized gastric neoplastic tendencies. In attempting to demonstrate, however, that polyps are precancerous lesions it should be kept in mind that gastric polyps are very uncommon lesions, which are seen even less frequently than stomach cancer. Peptic ulcers, on the other hand, affect as many as 10 per cent of the population.

Ming and Goldman [63] examined 90 polyps removed from 49 patients, 76 of which were classified as regenerative (hyperplastic) polyps lacking a distinct neoplastic nature. Of the remaining 14, 10 adenomatous polyps were considered to be truly neoplastic and in four of these (14 per cent), focal malignant changes were demonstrated, and these generally had marked hyperplasia and metaplasia. Additionally, there was a co-existing adenocarcinoma of six of the 49 patients.

Tomasulo [64] studied 97 cases of gastric polyps and also differentiated between those which were hyperplastic and adenomatous. Overall, 34 (35 per cent) were found incidentally during gastrectomies for gastric carcinoma and five (5 per cent) were incidental findings during gastrectomies for peptic ulcers and other diseases. Overall, 59 per cent of the adenomatous polyps and 28 per cent of those which were hyperplastic were associated with gastric cancer, and changes identified as carcinoma in situ were seen in five of 23 cases of adenomatous polyps. The authors conclude that adenomatous gastric polyps may be precursors of invasive gastric carcinoma and express the opinion that those who say they are not may be basing their evidence on an analysis which has not differentiated between the different histological types.

Some investigators have also differentiated between polyps of different sizes. Monaco et al. [65] studied 153 patients, 15 (10 per cent) of whom had large polyps greater than 2 cm. in diameter, which is generally considered the type most likely to undergo malignant transformation. While there was marked epithelial atypicality and small foci of carcinoma-in-situ in nine of these 115 cases, none showed metastases and the authors conclude that "there is no evidence in our series that adenomatous polyps progress to the usual invasive infiltrating carcinoma or that the residual stomachs are more prone to the development of carcinoma", which disagrees with the conclusions of Berg [62] and Tomasulo [64]. Marshak and Feldman [66] reviewed the literature and concluded that estimates of the transformation of benign gastric polyps to a malignancy varied from 0-51 per cent and they felt that the disagreement may be due to differences in terminology and pathologic

criteria. Based on available evidence, they recommend that, if on roentgenologic examination the polyp measures less than 2 cm. in diameter, conservative treatment should be undertaken. If the polyp is smooth and greater than 2 cm. in diameter, however, it is usually benign but since there may be such a finding with polypoid carcinoma, surgery is indicated.

Achlorhydria is probably important as a reflection of the integrity of the parietal cells, in which hydrochloric acid is produced. Gastric mucosal atrophy is therefore generally accompanied by a state of a- or hypo-chlorhydria. There are some who believe, however, that gastric atrophy, which leads to achlorhydria, may actually increase susceptibility to carcinogens which might otherwise be destroyed by the normal pH in the stomach. At any rate, numerous studies have indicated that achlorhydria is, in many cases, concomitant with gastric atrophy and cancer.

For instance, Comfort et al. [67] determined that mean gastric secretory activity was lower at a mean interval of 11.2 years prior to the diagnosis of stomach cancer. It was actually lower as early as the third decade of life, but the decrement was more marked in the younger decades. The authors express the opinion that atrophy of the gastric mucous membrane is responsible for this decreased gastric acidity and point out that gastric cancers develop most often in stomachs with lower than normal mean secretory activity, many of them diseased with gastritis and peptic ulcers.

Stempien et al. [68] obtained quantitative estimates of gastric acid secretion among patients with numerous conditions including superficial gastritis, gastric ulcer, and atrophic gastritis. They found,

however, that only 4 per cent of patients with atrophic gastritis were hyposecretors, compared with 17 per cent among those with normal mucosa, and 28 per cent of the patients with gastric ulcers. Surprisingly, also, their series indicated that, among patients with ulcer and atrophic gastritis, 28 per cent and 24 per cent, respectively, were hypersecretors. Pastor and associates [69] avoided the problems of cross-sectional determinations and conducted two 10-year retrospective cohort analyses on Japanese of both sexes. In the first, which included 7,000 people, they determined that males with low serum pepsin levels experienced an age-adjusted stomach cancer incidence three times higher than those with normal secretion, although this difference was not found among women. The second study involved 1,250 Japanese and they found that, in general, persons with achlorhydria had a significantly higher age-adjusted incidence of gastric cancer than those with normal levels. Additionally, almost 700 patients had both tests and it was found that the highest incidence occurred among those with both low pepsin levels and achlorhydria.

Although the site of production of intrinsic factor (IF) which is necessary for absorption of Vitamin B₁₂, without which red blood cells do not properly mature, is presently unknown, there is some recent evidence [70] that it is produced within parietal cells. In the absence of IF, pernicious anemia develops. It would therefore not be unreasonable to find, simultaneously, achlorhydria and pernicious anemia in some gastric cancer patients, especially when the gastric cancer has been preceded by chronic atrophic gastritis, which is characterized by progressive and irreversible atrophy of the glandular epithelium of the stomach. In addition, atrophic gastritis is believed by some to be a precursor of gastric carcinoma.

Sivralla and Seppala [71] conducted a follow-up study of 53 patients with biopsy evidence of atrophic gastritis among whom there was no sign of gastric carcinoma on the basis of roentgenologic and gastroscopic examination. As controls, they chose 210 patients for whom gastroscopic examination revealed no signs of gastric carcinoma, gastric ulcer, or benign tumor and among whom the gastric mucosa appeared normal. The controls and cases were very similar in sex and age distribution and in the follow-up period (5.8 years for cases and 6.0 years for controls). Of the 52 cases, a total of 20 either died during the observation period or refused re-examination, with 33 undergoing re-examination at the end of the follow-up period. Unfortunately, the controls were not re-examined, and the investigators apparently relied on the development of gastric carcinoma among the controls to somehow come to their attention.

Sign of gastric carcinoma appeared in five of the cases, four of whom died during the follow-up period and one of whom was diagnosed as having gastric carcinoma at re-examination; none of the controls showed signs of gastric cancer. In only one instance, however, was the diagnosis of carcinoma confirmed by histologic examination, while among the remainder the diagnosis was based on roentgenological, gastroscopic, or esophagoscopy examinations or upon macroscopic examination at autopsy. Because of these limitations, the authors hesitate to conclude definitely that atrophic gastritis is a precursor of the malignant lesion, although they suggest that carcinoma might develop from advanced atrophic gastritis with metaplasia.

Kaplan and Rigler [72] examined a series of 43,021 consecutive autopsies at the University of Minnesota during the period 1915-43 for

the co-existence of pernicious anemia (PA) and gastric carcinoma. The diagnosis of pernicious anemia was based on departmental records when it had been made prior to death. The investigators were concerned that the diagnosis of PA may have been discarded or unrecognized if a carcinoma was found, so they essentially took a sample of autopsies to determine the proportion of occult cases. Diagnosis of PA, for this sample, was based upon information collected about the patient during his lifetime, since the best post-mortem evidence of the disease would come from an examination of the bone marrow which undergoes rapid post-mortem autolytic changes. The results indicated that in 293 cases of pernicious anemia, 36 (12.3 per cent) also had carcinoma of the stomach. This proportion of stomach cancer was more than three times as great as the existence of carcinoma in the remaining autopsy population of similar age.

In a pair of companion articles [73, 74] Morson first attempted to establish the presence of intestinal metaplasia in patients with duodenal and gastric ulcers and gastric carcinoma and determined that intestinal metaplasia was most common in stomachs removed because of carcinoma (92 per cent), compared with those removed for gastric ulcer (82 per cent) and duodenal ulcer (65 per cent). In cancer stomachs, the metaplasia was fairly evenly distributed, while it was most common at the pylorus in ulcer stomachs. However, the mean ages, and presumably the age distributions, differed in the three groups and, while there was no adjustment for these differences, Morson cites other studies where this was done and there was still more intestinal metaplasia in cancerous, compared with non-cancerous stomachs.

In the second paper, Morson demonstrates that carcinoma can arise from areas of intestinal metaplasia, which was observed in 33 per cent of 107 gastrectomy sections.

SUMMARY OF MAJOR FINDINGS

1. International Rates
great variability, with highest rates in Japan, Russia, Eastern Europe, and South American
2. National Rates
great substantial variability, with highest rates in North Dakota and lowest in South Carolina
3. Sex Ratio (Male:Female)
approximately 2.0
4. Social Class
decreasing rates as social class increases
5. Religion
no major difference aside from differences in ethnicity and social class
6. Migrant Studies
first generation migrants generally have rates closer to home, rather than host, country, but second and third generations gradually approach rates of host country
7. Dietary Factors
negative association with vegetable consumption, positive association with highly salted foods, and possible protective effect of antioxidants, as well as possible association with nitrosamines
8. Blood Type
slightly higher among those with blood type A
9. Alcohol
no apparent association
10. Tobacco
equivocal findings, weak association, if any
11. Soil Type
possible association, but findings essentially unexplained
12. Occupational Studies
inconclusive, although may be elevated among metal products workers, possibly associated with high dust levels

PATHOLOGICAL CONSIDERATIONS

Histologic Type

By far, the most common histologic type of stomach cancer is adenocarcinoma, implying involvement of the glandular epithelium, and estimates of the proportion of all gastric cancers which are of this type range from 70-90 per cent. Ming [75] has summarized the results of numerous surveys (Table 11) and has determined that, on the average, adenocarcinomas account for 88 per cent of all stomach tumors, whether benign or malignant, followed by lymphomas (3 per cent), and leiomyosarcomas (1.7 per cent). In total, these three tumors account for 93 per cent of all stomach tumors, and almost 100 per cent of all malignant ones. Stout, [76] however, who is probably the most frequently quoted authority on stomach cancer, is of the opinion that the histological classification is "hopeless and unrewarding", since almost all stomach cancers involve mucous secreting glands or pits and the histological classification, which presumably differentiates between different tumor types, becomes very arbitrary.

Lauren, [77] in 1965, citing Stout's dissatisfaction, proposed a new classificatory system which he considered to be histo-clinical in nature. According to this system, there are two main types of gastric carcinoma - intestinal and diffuse - and classification of a tumor into one of these two types is based on general and cellular structure, secretory properties, mode of growth, and clinical features. A summary of the characteristics of intestinal and diffuse type gastric carcinomas is presented below:

Table 11

TUMORS OF THE STOMACH

Malignant Tumors	Stout	UMH*	McNeer and Peck	Marshall	Total	Percent Combined Series
Carcinoma	470	310	1023	1567	3970	87.9
Carcinoid	5	3	3		11	
Leiomyosarcoma	24	13	24	16	77	1.7
Rhabdomyosarcoma	1				1	
Lymphoma	39	23	39	35	136	3.0
Plasmacytoma	2	1			3	
Kaposi's disease	1				1	
Total	542	350	1689	1613	4199	93.0
Benign Tumors or Tumor-like Lesions						
Polyp	32	20	51	37	140	3.1
Leiomyoma	39	16	9	28	92	2.0
Vascular tissue tumors	8	1	1		10	0.2
Nervous tissue tumors	4		3		7	0.2
Lipoma	1		3	2	6	0.1
Fibrous tissue tumors		2			2	
Heterotopic pancreas	6	1	1	12	20	0.4
Enterogenous cyst		1	1		2	
Inflammatory lesions	19	4	7		30	0.7
Miscellaneous			3	3	6	0.1
Total	109	45	39	82	315	7.0
Series Total	651	395	1768	1700	4514	100.0

*The University of Maryland Hospital (series not previously reported)

from [75]

1. Intestinal type: distinct, large, glandular lumens with glandular structure rarely completely absent; cells large and clearly defined with large nuclei and morphologic variability; cells lining the glandular lumens are well polarized columnar cells; few mucous secreting cells; spread to a clearly and often distinctly defined area; spread not wider in the mucosa than above the infiltrating part of the tumor.
2. Diffuse: glandular lumens are rarely seen and cells are scattered; cytoplasm indistinctly defined and cells are more uniform; nuclei small and more regular in form; cells lining the lumen are unpolarized and randomly grouped; secreting cells very extensive; wider spread inside the mucosa; spread not well defined.

In a series of 1,344 patients, Lauren found 53 per cent intestinal types, 33 per cent diffuse, and 14 per cent heterogeneous in composition. He then correlated the two main types with sex, age, and other characteristics of the disease and found that 65 per cent of the intestinal type carcinomas and only 54 per cent of the diffuse occurred among males. The mean age of patients with intestinal type was 55.4 while it was quite a bit lower - 47.4 - for patients with diffuse type. Both mean ages, however, are lower than the general estimates made by other investigators and Lauren did not further analyze mean age by sex. The age distributions also differed, with a greater proportion of diffuse patients below the age of 50 and a smaller proportion older than 60.

The mucosa in the immediate vicinity of intestinal-type carcinomas was less frequently normal than among the diffuse types, and a greater proportion of intestinal types (88 per cent) exhibited gastritis and intestinal metaplasia in the surrounding mucosa and also intestinal metaplasia. There was no correlation between the two main types and the site of the tumor within the stomach, but the prognosis was slightly better among those with the intestinal type. Lauren concludes that the two main types, "at least to some extent are caused by different aetiologic factors and that they differ pathogenetically as well".

Munoz and Collelly [78] were interested in determining whether Lauren's two main types differed etiologically, and whether the decline of gastric cancer rates within the U. S. was related to these types. They slightly modified Lauren's classification and assigned 127 histologically confirmed gastric cancer cases from Hartford Hospital during two time periods - 1940-44 and 1960-64 - into one of three categories: intestinal (well-differentiated) adenocarcinoma, diffuse (undifferentiated) adenocarcinoma, and "others". In addition, cases were classified by age, sex, and place of birth, the latter to differentiate between high and low risk birth areas.

There was a total of 62 native-born and 65 foreign-born cases, and 74 intestinal, 45 diffuse, and 8 "others". Intestinal type carcinoma was statistically significantly more common among those from high risk birth places. Although the authors do not explicitly specify how risk was determined, the foreign-born group included 44 Europeans and 15 Russians and Poles. This difference persisted after controlling for sex and time period. The age and sex distributions during the two time periods were similar and, although there was a decrease in the proportion of intestinal types between the two periods under study, the decrement was not statistically significant. They also determined that the ratio of intestinal to diffuse increased with age in both sexes and in both risk groups and corroborated Lauren's finding that intestinal metaplasia was significantly more common among those with intestinal type carcinoma.

Munoz and Collelly, like Terris [33] were of the opinion that declining U. S. gastric cancer mortality rates could not be explained by the decreasing proportion of foreign-born in this country. An

indirect age-adjustment was then carried out to determine morbidity rates by histologic type for the two periods, although the method of calculation is somewhat unclear and no adjustment was made for nativity composition, which would seem to be important in view of their finding that the intestinal type was more common among the foreign-born, especially since the proportion of cases from high risk areas in each of the time periods is not presented. Nevertheless, the authors explain that the 38 per cent drop in gastric cancer incidence during the two periods is accounted for mostly by a drop in the intestinal type. It seems questionable to calculate adjusted rates and draw inferences to the general population, based only on their hospital sample, from which a large proportion of apparent cases without histologic confirmation were excluded, especially if there is some selective difficulty in making one or the other type of diagnosis. The authors conclude that the "decline in gastric cancer incidence ... is related to a reduction in the frequency of intestinal type carcinoma. Since this type is also related to intestinal metaplasia, the etiology of the latter should be investigated".

Munoz et al. [79] conducted another study, based on Lauren's classification, to determine if there were differences between high and low risk areas. This one was based on 322 cases of gastric cancer from Columbia and Mexico, and assignment to a high or low risk area was based on a single estimation, by another investigator, of the rates in the cities from which the cases were drawn. While the mean age of the patients was similar in both risk areas, neither the age nor the sex distributions are presented, although male:female ratios for both area and type are freely used. The results indicate that a greater

proportion of cases from high, compared with low risk areas, were of the intestinal types (51.8 per cent vs. 35.9 per cent).

Location

Estimates of the site of the tumor within the stomach vary slightly, and these estimates are doubtlessly complicated by the fact that, by the time the tumor is discovered and examined, it may be very large and probably involves more than one region. Ming [75] has collected estimates from more than 7,000 examinations by different investigators and found the following mean ranges - pyloric: 47-50 per cent, lesser curvature: 13-39 per cent, cardia: 10 per cent, diffuse: 6-8 per cent. These findings generally agree with those observed by Stout [76] (Figure 2), and it is clear that the most common site is the distal portion of the stomach. Crane et al., [80] for instance, found that 75 per cent of the cases in their series of over 1000 occurred in the pyloric region.

Metastases

Determination of tumor spread depends, naturally, upon its site and stage, although there are fairly clear patterns, based on the data presented by Stout, [76] Ming, [75] and Crane [80]. The most common metastatic sites are - perigastric lymph nodes: 80-90 per cent; peritoneum, omentum and mesentery: 20-40 per cent; liver: 15-50 per cent; pancreas: 17-20 per cent; lung: 30 per cent.

Metastases to the stomach from other sites, or direct invasions, are very rare, and estimates of their occurrence are one per cent or less.

Figure 2

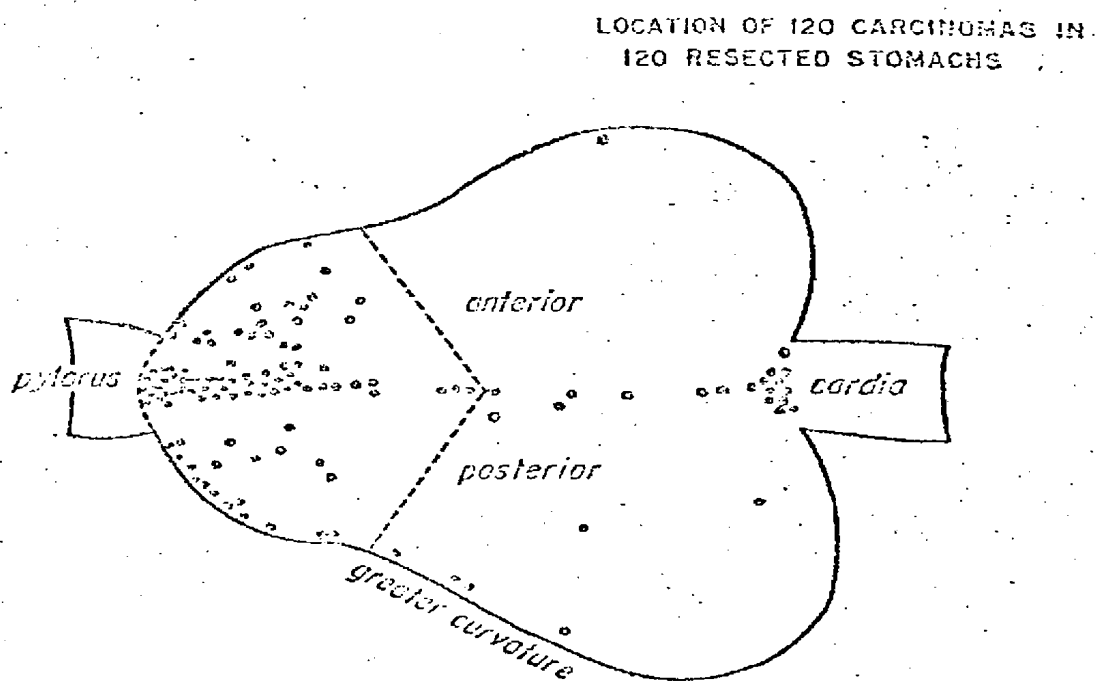
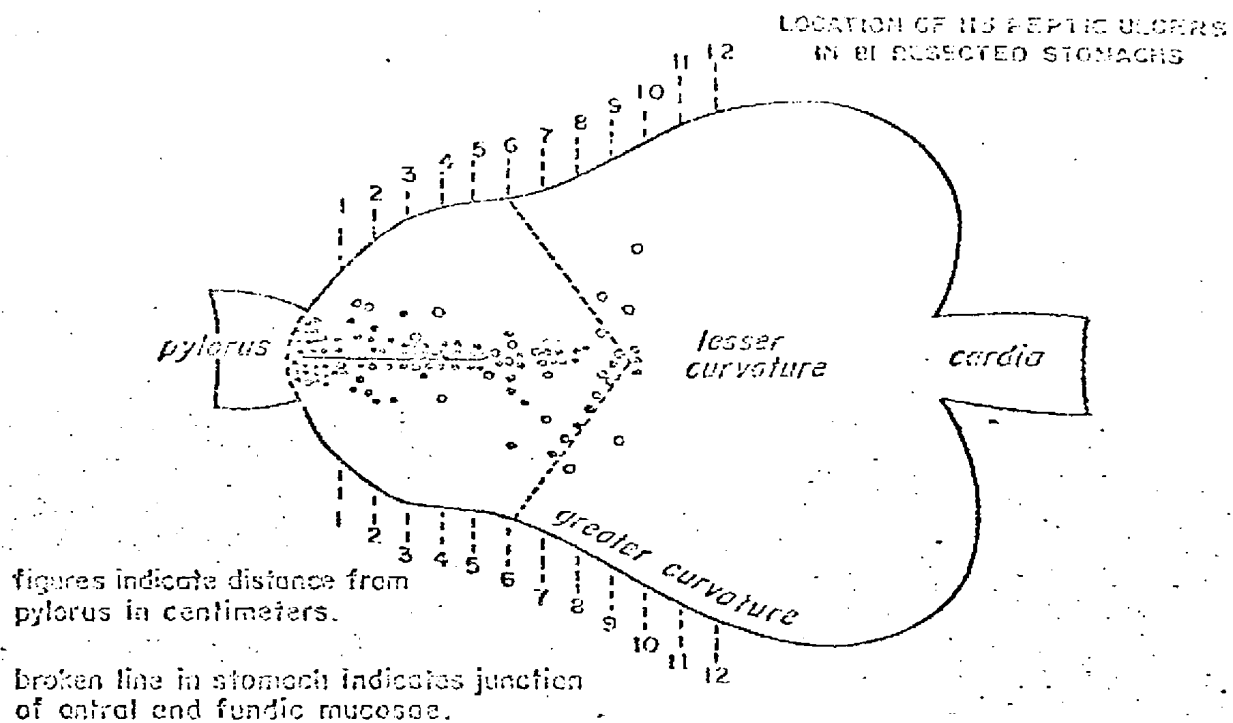


Figure 20. Two diagrams illustrating the location in the stomach of 61 consecutive cases of gastric ulcer and 120 cases of gastric carcinoma. (Figure 1 from Stout, A. P. Tumors of the stomach. Bull. New York Acad. Med., 23: 101-103, 1947.) A. F. I. P. Acad. No. 219459 43.

from [76]

Prognosis

The outlook for victims of stomach cancer is very bleak, and prognosis is apparently not improving very much with time. While survival rates depend, to some degree, upon age, sex, site, extent of disease at diagnosis, and treatment, the picture is, overall, very dismal. Based on data from the National Cancer Institute, [2] the overall five-year relative survival rate, adjusted for mortality, among non-diseased people of similar age, race, and sex distributions, is only 12 per cent. The median survival time is approximately six months, even if the patient is less than 45 years of age. About half of all stomach cancer patients receive no treatment, and among those who do, surgery is the usual treatment. This low treatment rate is due to the fact that half of all cases are diagnosed at a stage beyond localized or regional involvement. The best prognosis is found among patients diagnosed in a localized stage and who are treated surgically, among whom the five-year relative survival rate is 50 per cent, although this group accounts for only about 12 per cent of all cases. Similar survival patterns were found in England [81].

CARCINOGENESIS

The field of carcinogenesis is very broad and encompasses many different areas, such as the events which occur at the cellular, sub-cellular, and molecular levels; the histologic characteristics of malignant growth; and the results of animal experimentation with specific carcinogens, as well as their mode of action. Unfortunately, despite the tremendous efforts expended thus far, little is definitively known about the carcinogenic process. This very brief review will stress the broad concepts and attempt to establish the plausibility, based mainly on animal studies, of the existence of a chemical carcinogenic process, within the rubber industry, which may be responsible for the greater than expected number of cases of gastric cancer.

Histologic Characteristics

There are innumerable definitions of neoplasia, but perhaps the simplest and most appealing is one offered by Hopps [82]: "neoplasia is a new growth of tissue, autonomous in nature, serving no useful purpose, obeying its own laws without respect for the organism as a whole, and growing at the expense of, rather than for the benefit of, the body."

This definition, however, describes the entire neoplasm. The next question is: what are the characteristics of a neoplastic cell compared with a normal one? Robbins and Angell [83] have summarized these attributes, and there seems to be general agreement among pathologists

concerning the behavioral characteristics of cancer cells: loss of or decreased adhesiveness, loss of contact inhibition, increased motility, increased contact guidance, and synthesis of enzymes or metabolites which may be injurious to normal tissue and which increase penetrative ability.

Normal adhesiveness between cells is dependent upon certain structural and electrical properties of cells. Desmosomes normally anchor adjacent cells and contact is strengthened by anionic bonds between cells, for which calcium binding by the cell is essential. In neoplastic cells, desmosomes are either absent or substantially reduced in number, and this is coupled by the inability of cancer cells to bind calcium, which results in the presence of negative charges, which repel each other, on the outside of every cell. These alterations lead to decreased adhesiveness.

One of the fundamental characteristics of normal cells is the inhibition of growth and mobility when they make contact with other cells. Cancer cells, on the other hand, have not only lost this contact inhibition, but there is evidence which indicates that mobility and growth are actually increased when they come in contact with normal cells. Even in the absence of contact with normal cells, however, cancer cells have been shown to be more mobile and more capable of rapid migration than most normal cells, with a few exceptions, such as macrophages. However, the very mobile normal cells are generally not capable of mitotic divisions, so the combination, in cancer cells, of increased mobility and retention of mitotic ability facilitates penetration and invasiveness.

Normal cells generally grow in an orderly fashion along strands of connective tissue in vivo, or along grooves in a glass culture dish in

vitro. If cancer cells destroy these connective tissue strands, they grow in a disorganized mass. If these strands are present, however, cancer cells will exhibit a greater than normal contact guidance which gives directionality to its mobility, thereby increasing its invasive and penetrating capacity. There is also fairly good evidence, although total agreement is lacking in this aspect, that cancer cells are capable of synthesizing proteolytic substances, such as hyaluronidase, which destroys connective tissue substance in preparation for invasion by the cancer cells. It has also been postulated that they synthesize toxins which are capable of destroying normal cells, which enhances the propagation and spread of cancer cells.

Metastasis, or spread of cancer cells, is considered the most serious complication, because surgical removal of a non-metastasized cancer, even though it is not encapsulated as is a benign neoplasm, generally results in a fairly good prognosis. In the neighborhood of the primary growth, metastasis generally is accomplished by direct invasion of adjoining tissue, which is enhanced by the increased mobility and penetrance of cancer cells described above. This often leads to penetration of blood or lymph vessels, resulting in hematogenous or lymphatic metastases, respectively. The cancer cells then lodge in new tissue, often far removed from the primary site, which is called secondary foci or foci of metastases. Once a cancer has metastasized, the prognosis is drastically impaired. Metastases are exacerbated by another feature of cancer cells, namely, their differentially high reproductive rate, which gives the appearance of being essentially autonomous in nature. This increased rate of growth is especially apparent in undifferentiated (or anaplastic) malignancies, as opposed

to the well-differentiated type. It should be remembered, however, that despite the rapid rate of growth of cancer cells, there is a very long interval, measured in decades, between initiation of the process and clinical manifestations.

Chemical Carcinogens

Before proceeding to a discussion of chemical carcinogens, it would be best to briefly describe some terminology and alternative hypotheses of the carcinogenic process. Direct acting, or proximate carcinogens are those which do not require host enzymatic metabolism to generate the key reactive substance, or ultimate carcinogen.

Many synthetic and industrial chemicals are proximate carcinogens.

Pre-carcinogens, however, become active only after metabolic conversion by the host and are not carcinogenic in their native form. Included in this group are most chemical carcinogens. Proximate carcinogens are generally highly reactive substances, which is almost a requirement of industrial chemicals, since they are normally quickly deactivated. If they are not deactivated, however, they become highly carcinogenic.

Pre-carcinogens can also be either activated or inactivated, a process which generally occurs in the liver, which contains the enzyme systems necessary for metabolic conversion. In fact, it is believed that all carcinogens can be activated by the liver and also by other organs, such as the lung, kidneys, and placenta, among others. Note, however, that proximate carcinogens do not require activation, while pre-carcinogens do, although both may be deactivated.

There is another important general concept of the difference between initiators and promoters. An initiator is capable of initiating

the carcinogenic process by itself, and is therefore a true carcinogen, but the process is often very slow. Carcinogenesis can be hastened, however, by application of a promoter, or co-carcinogen, which is itself generally not carcinogenic. Application, to a site, of a promoter before the addition of the initiator generally does not result in cancer, unless the interval is very short, in which case the promoter may still be active. This hypothesis is called the "Two-Stage Theory of Cancer Induction" although it should be remembered that the initiator, by itself, is capable of inducing carcinogenesis in large enough doses. Therefore, while the initiator may or may not require a promoter, promoters can do no damage in the absence of initiators since they are not independently carcinogenic.

Regardless of the pathway or mode of action of a specific carcinogen, the cellular alteration must be heritable. This alteration then becomes capable of storage, replication, and transfer, to all new cells and indeed new generations of cells may incorporate additional changes which also become heritable and further increase the difference between normal and neoplastic cells. The mechanism of action of alteration, however, is presently moot, with theorists divided between two alternative pathways: genetic or epigenetic. Proponents of the genetic theory insist that cancer induction results from an interaction of the carcinogen with DNA, resulting in a permanent alteration in the DNA information which, naturally, becomes heritable. This is generally believed to occur by a binding of the carcinogen to nucleic acids, resulting in a permanent alteration of the base sequence. According to this theory, initiators are capable of inducing just a few mutations which are not capable of autonomous growth or replication, but the application of a

promoter, which may lead to additional alterations in the presence of the promoter, may lead to heritability and autonomy. The epigeneticists, on the other hand, believe that the primary mechanism involves some alteration in the cytoplasmic feedback mechanism, perhaps by some alteration of messenger RNA, which may lead to a permanently altered but stable metabolic pathway. According to this theory, the carcinogenic process is reversible because the basic alteration is in the gene expression and not in the genome itself.

In a classic review article, Miller,[84] who is one of the pioneers in the field of carcinogenesis, has reviewed the pertinent findings to date. He notes that almost all chemical carcinogens, with the exception of alkylating agents (such as uracil mustard) are pre-carcinogens which require activation before they become ultimate carcinogens. The single basic characteristic of almost all ultimate carcinogens, whether or not they require activation, is their strong electrophilic property, which enables them to react with nucleophilic substances such as nucleic acids and proteins. For instance, it has been shown in vivo and/or in vitro that the aliphatic agents, including nitrosamines, are alkylating agents either in their native form (proximate carcinogens) or after enzymatic or non-enzymatic activation (pre-carcinogens) which interact with nucleic acids and protein. Aromatic carcinogens, on the other hand, have not been shown to bind with nucleic acid in vivo, but the evidence is very convincing that they form strong electrophilic reactants which can displace, at least in vitro, the weaker electrophiles such as H^+ . Despite the magnitude of the effort invested in elucidating the mechanism of chemical carcinogenesis, however, Miller concludes that "in no case of chemical carcinogenesis do we know unequivocally the nature of the

molecular target(s) critical to the induction of that carcinogenic process". The known carcinogens of greatest interest within the rubber industry are the aromatic hydrocarbons (including 3,4 benzpyrene), nitrosamines, and asbestos. The remainder of this discussion will focus on these agents.

It is generally believed that the aromatic hydrocarbons are precarcinogens which require activation. Kellerman, et al. [85] have shown that the ultimate carcinogen is probably an epoxide which is formed in the presence of the inducible enzyme aryl hydrocarbon hydroxylase (AHH), which shows increased activity after administration of numerous chemical agents, including benzpyrene. They have further demonstrated that the U. S. white population can be divided into three phenotypic inducibility groups - high, intermediate, and low. The degree of inducibility is presumably under genetic control with two alleles at a single locus, resulting in homozygous high and low groups and the heterozygous intermediates. They then determined AHH activity in cultured leukocytes from three different groups - histologically confirmed cases of bronchogenic carcinoma, cases with a range of different types of tumors, and a healthy control group. While no mention is made of confounding factor distributions in the three groups, this presumably is not an important factor in this type of study. They found highly statistically significant differences, in the phenotypic distribution, between lung cancer cases and healthy controls: 30 per cent of the cases had high inducibility compared with 9.4 per cent of the controls, while only 4 per cent of lung cancer cases had low inducibility against 45 per cent of the controls. The differences between the "other" tumor group and healthy controls were not significantly different. They

conclude that this evidence supports the hypothesis that susceptibility to lung cancer is inherited. Unfortunately, these results have not been duplicated after attempts by numerous investigators.

There is fairly good evidence the polycyclic hydrocarbons require suspension in particulate matter to be carcinogenic. Winkelstein and Kantor [86] have studied the relationship between suspended particulate air pollution and gastric cancer in Buffalo, New York, among males and females 50-69 years of age. According to the authors, the finding that mortality rates from gastric cancer were twice as great among residents of high, compared with low, areas of suspended air pollution, is independent of socioeconomic and ethnic effects. To eliminate the effects of a large Polish population, the investigators assumed that this group would have a rate (70/100,000) $2\frac{1}{3}$ times as high as the average death rate among whites in the age range under study, then from a census estimate of the proportion of the total population of Polish origin, they calculated the number of deaths expected among this ethnic group. These deaths were subsequently removed from the numerators and denominators which were used to estimate mortality experience. This appears to be a novel approach to the problem which may or may not be methodologically sound, but their estimate that a mortality rate of 70/100,000 is $2\frac{1}{3}$ times the average is apparently not corroborated by the evidence which they themselves present, indicating that, among males, as the four-component spectrum of pollution levels from low to high is traversed, the rates are approximately 25, 40, 50 and 75/100,000.

At any rate, the evidence indicates that polycyclic hydrocarbons, such as benzpyrene, must be suspended in particulate matter to be

carcinogenic. Both the carcinogenic hydrocarbons, and particulate matter in the form of carbon black and perhaps talc, are abundantly present within the rubber industry.

Matolo, et al [87] studied the incidence of gastric cancer in two coal mining counties in Utah and compared these rates with those found in one non-coal mining county and with the entire state. They found that the incidence of gastric cancer in coal miners was 15 times higher than in non-coal miners in the mining counties and 40 times higher than in non-miners in the entire state of Utah. The authors stress the fact that coal soot has a rather high benzpyrene content, and contains both large and small particles to which this hydrocarbon may adhere. They conclude that there is a statistically significantly higher incidence of gastric cancer in the two coal-mining counties, and add that coal mining, and the extensive use of soft coal by both miners and non-miners for heating and cooking, might be an etiologic factor. Creagan, et al., [88] however, suggest that the correlation may be with socioeconomic class rather than with exposure to coal mining and its use.

In a study on the relationship between atmospheric pollution and mortality from certain chronic diseases in England and Wales, however, Percy Stocks [89] found that intestinal and gastric cancers were related significantly with smoke containing many different types of polycyclic hydrocarbons. Stocks further states that this relationship can only be partly explained by social differences in the populations concerned.

There has been much research conducted on the carcinogenicity of many different types of nitrosamines, since 1956, when Magee and Barnes [90] discovered the development of malignant liver tumors in rats fed

dimethylnitrosamines. In subsequent animal investigations, these compounds have been shown to be very potent carcinogens at many different sites, including the trachea, lung, kidney, bladder, and stomach in many mammalian species, fish, and birds. Nitrosamines have been shown to be mutagenic and teratogenic as well as oncogenic. It has been reported that nitrosamines can be formed in vivo in the stomach via an acid-catalysed reaction between a secondary amine and nitrite, and also by a bacteria-catalysed reaction at any site in the presence of a secondary amine, and nitrate or nitrite. Hill, et al., [91] studied mortality from gastric cancer in ten towns in England - one experimental town with a mean nitrate content in drinking water of 90 mg/liters and 9 control towns with a mean content of about 10 mg/liters. While mortality from all malignant neoplasms combined was significantly lower than expected, mortality from stomach cancer was significantly higher for both sexes taken together, with the greatest excess in females. The authors hypothesize the formation of nitrosamines in the bladder which subsequently induces gastric cancer via a systemic reaction. A number of investigators [92,93] have expressed the opinion that industrial workers are at particularly high risk of exposure either to nitrosamines or their precursors.

Numerous studies have shown that pleural mesothelioma and other pulmonary diseases are statistically correlated with asbestos exposure. Recently, a number of studies have suggested that gastric carcinoma, as well, may be associated with exposure to asbestos and asbestos-containing talc (94-96, 131-139), and talc is widely used during tire production. Industrial hygienists at the Occupational Health Studies Group have estimated that the asbestos content of talc used in the

industry may have been fairly high in the past. Merliss [94] has suggested that the high incidence of gastric cancer in Japan may be due to treatment of rice with talc, although others believe that the increased Japanese incidence may be due to the formation of nitrosamines, as described above. In a study of talc miners in New York State, Kleinfeld, et al. [95] found a significantly higher than expected mortality from gastrointestinal malignancies. Other studies, however, disagree with the conclusion that gastric carcinoma is associated with exposure to asbestos.

In an interesting study which bears on these matters, an English group [96] used an analytical electron microscope to study the particulate material present in stomach tumors in Japanese males. Their analysis indicated the presence of Kaolin, aluminum and calcium silicates, talc, and some types of asbestos fibers, including both amphibole and chrysolite. Unfortunately, the authors do not mention anything concerning the levels of these substances in "control" tissues, nor do they discuss the implications of these findings or their relationship to carcinogenesis.

REVIEW OF MAJOR OCCUPATIONAL STUDIES

Awareness of occupationally related diseases reaches far back into antiquity, and scientific investigations to determine their causes have been conducted, with varying degrees of success, for hundreds of years. Included in this chapter will be a review of the methodologies used to determine unique disease occurrences in three occupational groups - steelworkers, asbestos workers, and uranium miners. These have been chosen because of the thorough manner in which the studies have been conducted and because it was felt that they are fairly representative of the methods generally used in occupational studies. The purpose of this short chapter, it should be kept in mind, is not to present results or conclusions, but rather to illustrate the methodologies generally employed by investigators to establish relationships between disease and exposure in occupational groups.

Steelworkers

These studies, conducted by a group from the University of Pittsburgh Graduate School of Public Health, in collaboration with the U. S. Public Health Service and the National Cancer Institute, are both recent and exhaustive, and are very similar to our own rubber study, within which this present investigation is being conducted. For this reason, all papers thus far published will be reviewed in detail.

The introductory paper [97] begins with a general description of the methodologic approaches used in long-term industrial studies, and includes an historical review. The authors caution the reader about an

ignorance of selective factors, of major concern in studies of this nature, which may lead to biased estimates of disease occurrence, and also describe additional sources of bias, such as improper definition of the population-at-risk, or an inappropriate choice of comparison or referent group. As an illustration of the latter, the authors use the example of what we call the "healthy worker effect", which may lead to incorrect conclusions about the health status of an employed population.

To overcome these types of problems, they recommend longitudinal studies, although they note the impracticality of this approach for diseases with long latent periods, a category which encompasses essentially all chronic diseases and not only malignancies. They suggest instead, and themselves use, the retrospective cohort approach.

The cohort used for this study includes all men employed by three firms in 1953 in seven plants within Alleghany County, Pennsylvania. This cohort represents approximately 60 per cent of all men employed by the steel industry within the U. S. in 1953. In all, just under 60,000 steelworkers were included, and follow-up information on all but 97 (0.2 per cent) workers was obtained, with all deaths confirmed by death certificates.

Since analyses according to specific occupational history would routinely be performed throughout the course of the study, a method was needed which would assign each member of the cohort to his appropriate occupational group. As in our study, changes in job title terminology over the years, as well as different usage by each of the three firms involved, made this task more difficult. Accordingly, personnel offices at each plant were requested to provide a translation to currently used titles, and in this manner the 14,000 distinct titles

were reduced to 76 subgroups, and further into 10 basic groups, a procedure very similar to the one utilized by the rubber study.

Initial simple mortality analyses were based on SMR's, with expected numbers calculated from county rates, separately for whites and blacks.

Interestingly, the first more detailed mortality analyses [98] were correlated with socio-economic, rather than physical, factors. In 1947 an income index, used to determine wages, was introduced into the industry. Each job, according to this system, is assigned a total score and a corresponding hourly wage. The total score comprises twelve elements which assess skill, responsibility, effort, and working conditions on the job. Because this total job score is the industry basis for the determination of salary level, it concomitantly measures income and reflects the education and work experience of the employee. Use of this total score avoids the problems caused by fluctuating economic conditions in that it remains relatively stable and is therefore a more reliable indicator of socioeconomic status than are the actual wages.

These scores were further categorized, for analytic purposes, into one of four groups. In general, a negative association was found between total job score level and mortality among whites. Additionally, the earlier reported excess non-white mortality was explained by job score level, and racial factors were therefore ruled out, an instance where the investigators did not stop at the holy duality (because all subjects in this study are male) but sought real explanations, other than the nebulous factors of race and sex, for their findings.

The next paper [99] in this series describes in detail the methods used for tracing large industrial populations over extended

periods of time. The authors stress the importance of determining the vital status of as large a proportion of the cohort as possible, because of the possibility of drawing erroneous conclusions or biased estimates of disease occurrence. They especially caution against relying on data only for those who remain in an industry, in which case total mortality will be understated. Additionally, distribution of cause of death will likely be different for those who remain within an industry compared with those who leave.

The investigators examine the operation of some of these factors within the present study, where 1381 of 4716 deaths, at the time of this analysis, among the cohort members, were unknown to the employers. The differential distribution of the unknown causes of death was striking - 45 per cent of deaths from malignancies, compared with 21 per cent of heart and circulatory disease deaths, were unknown to the employers. There was a racial difference as well, with employers unaware of 28 per cent of the deaths among whites and 36 per cent of deaths among non-whites.

They also indicate that employee age is itself a selective factor which may lead to biased estimates, because the pension system favors greater awareness, among employers, of deaths among older, compared with younger, employees.

The authors then review available sources of follow-up information including: the Social Security Administration, Veterans Administration, county death lists, city directories, and Internal Revenue Service sources, among others. The follow-up scheme is summarized in Figure 3, and Tables 12 and 13.

TABLE 12

Redmond et al.

Distribution of Steelworkers by Primary Source of Follow-Up and Race
(1953-1961)

Primary Source	Total		White		Nonwhite	
	No.	%	No.	%	No.	%
Total	24,970	100.0	21,437	100.0	3,483	100.0
Employee Record at Plant	3,500	14.0	2,835	13.3	645	18.5
County Death Lists (1953-1962)	1,137	4.6	943	4.4	191	5.5
R. L. Polk & Telephone Directories	3,557	14.2	3,263	14.9	349	10.0
Post Office	9,141	36.6	8,097	37.7	1,044	30.0
Internal Revenue Service	2,828	11.3	2,516	11.7	312	9.0
Social Security Administration	4,043	16.2	3,309	15.4	734	21.1
Telephone Contacts	504	2.0	383	1.8	121	3.5
Board of Public Assistance	56	0.2	23	0.1	32	0.9
Bureau of Employment Security	29	0.1	22	0.1	7	0.2
Bureau of Missing Persons	11	0.0*	8	0.0*	3	0.1
Other Sources	67	0.3	50	0.2	17	0.5
Not Located	97	0.4	70	0.3	27	0.8

* Indicates values less than 0.05%.

from [99]

TABLE 13

Redmond et al.

Distribution of Steelworkers by Primary Source of Follow-Up and Year of Separation

Primary Source	1953-1955		1956-1958		1959-1962	
	No.	%	No.	%	No.	%
Total	11,825	100.0	5,292	100.0	7,872	100.0
Employee Record at plant	91	8.4	690	12.8	1,829	23.2
County Death Lists (1953-1953)	472	4.0	377	7.1	293	3.7
R. L. Polk & Telephone Directories	853	7.3	965	18.2	1,735	22.1
Post Office	3,905	33.8	1,981	37.4	3,164	40.2
Internal Revenue Service	1,994	16.9	504	9.5	339	4.2
Social Security Administration	2,959	25.1	658	12.4	426	5.4
Telephone Contacts	342	2.9	91	1.7	71	0.9
Board of Public Assistance	42	0.4	9	0.2	5	0.1
Bureau of Employment Security	20	0.2	2	0.0*	7	0.1
Bureau of Missing Persons	8	0.1	3	0.1	0	—
Other Sources	42	0.4	11	0.2	14	0.2
Not Located	84	0.7	11	0.2	2	0.0*

*Indicates values less than 0.05%.

from [99].

In the fourth paper of this series [100], the authors describe the methods used to determine mortality by work area, a procedure which leads to the identification of general and cause-specific, high and low mortality risk areas within the plant, when compared with the experience of the total steelworker population. The authors again caution us about the attribution of unusual disease occurrences, within specific work areas, to environmental exposures without considering sources of non-etiological associations due to bias.

For instance, in using the total steelworker group as a referent, selection due to employability (healthy worker effect) is avoided, but selection for health within a specific work area is not, and, as a consequence, deficits or excesses within an area may be unrelated to exposures. Because little is known about these internal selective factors, much caution is suggested before drawing any conclusions of an etiological nature.

In all, 53 work areas were defined and workers were assigned to one of two groups - work area at initial observation in 1953 and areas in which at least five years had been spent by the end of 1961. Expected deaths within each work area were race - , age - , nativity - , and residence-specific, and were calculated on the basis of rates from the total steelworker population, which were then compared with observed rates within each area.

Analyses were first performed according to the categorization by work area in 1953, and these were followed by analyses of workers with a minimum of five years of experience within a specified work area. This second group was included because of the probability that disease response is a function of duration of exposure, in which case the first

type of analysis, by including men with very short exposure durations, may mask true differences.

In addition, because it was assumed that the mortality experiences of workers with long and short employment durations differed, the comparison group for those with five years of experience within an OT was comprised of steelworkers who had attained five years of employment within the industry prior to or during the period 1953-61.

Next [101], an earlier finding of a two-fold excess of respiratory cancer among men employed in the coke plant is examined, and a differential mortality analysis among whites and non-whites separately, by calendar period and by duration of employment in several specific areas within the coke plant, is performed. Once again, an internal comparison is made between the observed mortality experience during the period 1953-61, and expected mortality predicted by the age - , race - , and nativity-specific rates for the total steelworker population, within each of two work areas within the coke plant - coke oven workers and nonoven workers. Also, two different employment groups were examined - those employed in the coke plant in 1953, and those not employed in 1953 but with experience in the coke plant prior to that date. The latter group was included so as not to restrict subjects to those employed at a single point in time, among whom certain selective factors might be operating. In all, 3530 men were studied and it was found that the excess respiratory cancer was limited to men employed at the coke ovens. When this was further analyzed, it was found that among those working at the tops of the ovens there was a five-fold lung cancer risk and, of these, among those with five or more years of experience the relative risk was ten. Again, an earlier reported black-white difference

was explained by differences in work histories, which presumably indicates an environmental, and not a racial, difference.

This finding among Allegheny county steelworkers led to an additional study [102] in ten selected plants within the U. S. and Canada, in an attempt to establish confirmatory evidence for the excess risk reported above. The study subjects included men in these plants with coke oven experience during the period 1951-55, and the experience of this group was compared with the experience of a group of men employed at the same plant during the same period. Two controls were chosen for every case, matched on race and date of initial employment, and while two different matching schemes were used, the basic procedure was the same at all plants.

The analyses utilized various work areas within the coke oven area (full topside, partial topside, side oven) as well as varying employment durations, and contrasted the rates in these different groups with those of men employed in different work areas of the plant, with adjustments for specific plant, race, age at entry and calendar years of follow-up. In general, the conclusions reported earlier were confirmed by these studies, which also yielded a new finding of a kidney cancer excess among this group.

The next three papers in this series [103-105] examine disease occurrences within three specific groups of workers - crane operators, open hearth workers, and sheet and tin mill workers. In each instance, an appropriately chosen control group, from within the industry, was used for the estimation of relative risks. Cranemen were classified according to their most likely type of exposure (gaseous, particulate, gaseous and particulate, clean, unknown) and were compared with a group

of controls who were never cranemen. In addition, exposure duration estimates were utilized. It was found that men with particulate exposure had higher renal and cardiovascular mortality risks than men in other categories, and there was a generally increasing relative risk as exposure duration increased, with the expected exception of those who were employed in a "relatively clean" area. The last two studies were conducted in ways very similar to those already described, and need no further comment, especially since neither presents definitive conclusions.

Similarities between the steelworker and rubber worker have been noted throughout this review, although there is one major difference in the approach to "matched" studies. We generally identify individuals with a specific disease and compare them with appropriately chosen controls in the classic "case-control" mode, during which we look for differences in work histories which would indicate different environmental exposures, and from which we estimate relative risks. The steelworker group has chosen the follow-up (retrospective cohort) approach, in which their two groups are exposed - not exposed as of a certain date, from which more precise and direct relative risks can be calculated. Because our initial analyses were not performed by work area (OT), and because our initial identification of mortality excesses and deficits were not calculated according to work area, this approach would be more difficult within the rubber study.

Asbestos Workers

Lynch and Smith [106], in 1935, were the first to report the case of an asbestos worker with both pulmonary asbestosis and associated

carcinoma of the lung, and they speculated on the possible etiologic significance of asbestos exposure in pulmonary malignancies. Since this first report, many others have found the joint occurrences of these two conditions. In 1960, Wagner, et al. [107] identified 33 cases of pleural mesothelioma, a generally rare tumor, in an asbestos mining area in South Africa among both whites and blacks of both sexes. Of the 33 cases, the investigators were able to establish definite evidence of asbestos exposure among eight cases, and a probable exposure among another twenty.

Numerous more thorough studies followed these initial reports of the relationship between an occupational exposure and a malignancy. Doll [108], in 1955, cited autopsy data from England on persons known to have been employed at a large, unidentified, asbestos factory and showed that, of 18 cases of lung cancer among this group, 15 were associated with asbestosis. He then estimated the latency period among these 15 men by determining the elapsed time between first exposure and death, which varied from 16-36 years among those with associated asbestosis, while the exposure ranged only from 2-11 years among the three cases of lung cancer without asbestosis. All 15 men in whom both conditions prevailed had started work in the industry before 1921, and therefore had at least ten years of concentrated exposure before national standards were instituted in 1933.

Doll also used a prospective approach in his investigation, reported in the same paper, of 113 men employed for at least 20 years within the industry in areas of high asbestos exposure, based on personnel information supplied by the company under study. The group included some who were still active and others who were no longer

employed within the industry. The group was followed, and causes of death were determined from death certificate/autopsy information. This was followed by the calculation of an indirectly standardized rate, using the male rates for England and Wales as a referent. A total of eleven deaths due to lung cancer, with mention of asbestosis, was found, while none were expected. From these data, Doll concluded that asbestos workers experience a lung cancer risk ten times higher than the general male population, and that the risk became progressively lower as the duration of employment under dusty conditions decreased.

Selikoff [109], who has studied asbestos workers probably more exhaustively than any other investigator, studied and examined asbestos insulation workers in the New York - New Jersey area, where the first union was established in the late 1800's. He identified all 1522 men who were ever members of the union local under study during the period 1942-62, of whom 1258 were still alive at the start of the study in 1963. Over 90 per cent of this group, which included actives, retirees, and withdrawals from the industry, presented themselves for a history and physical examination.

Detailed work histories were solicited from the men. The information included exact type of work performed, use of protective respirators, prior health experiences, and smoking habits. This was supplemented with a physical examination which included x-rays. Overall, more than half of those examined had evidence of pulmonary asbestosis, and the proportion with this condition increased with increasing exposure, the latter having been categorized into five exposure levels. In addition, eleven cases of lung cancer were discovered during these examinations, all among men with 20 or more years of exposure within the industry.

Concentrating on the 632 men with 20 or more years of exposure among this group, Selikoff, in a subsequent analysis [110], calculated SMRs based on U. S. rates. Among the group under study, almost half (339) had 40 or more years of exposure, and, in all, the group had experienced 8738 man-years of exposure within the industry. SMRs of 700 for cancer of bronchus and pleura, and 300 for stomach and colorectal cancers, were reported, although the latter were based on small numbers.

Enterline [111] identified 2833 white males who had worked in the asbestos products (mainly textiles) industry between 1948-51 for 13 different manufacturers, using social security records. Deaths were identified from death claims made to the Social Security Administration and, of the 286 deaths so identified, certificates were obtained for 273.

The mortality experience of these asbestos workers was compared with the experience of cotton textile workers because the latter were thought to be engaged in work similar to that of asbestos workers and to have similar socio-economic status, without concomitant exposure. In all, 6243 cotton workers were included and cause-specific SMRs were presented. The all-causes SMR was 112 for asbestos workers and 88 for cotton workers, while the respiratory cancer SMR was approximately 200 among the former and 30 (7/25.6) among the latter.

Braun and Truan [112] undertook a cohort study after complaining about the absence, in prior studies, of a well defined population of asbestos workers and improper epidemiologic methodology. They identified an apparently exhaustive cohort of asbestos workers in Quebec, all of whom had at least five years of experience as of 1950. The cohort

included 6091 men, 133 of whom were lost to follow-up, with the remainder being followed for six years. During this period there were 187 deaths, of which nine were definite, and three highly probable, lung cancers. Members of the cohort were studied with respect to age, duration of employment, smoking habits, and a weighted exposure average, based on number of years spent at various dustiness levels. These exposure categories were determined from "consultations with persons familiar with the environment and conditions in the various work areas". Three levels were used, with category II considered to be twice as dusty, and category III three times as dusty, as category I, quite an assumption in view of the manner in which dustiness determinations were made.

While complaining about the paucity of epidemiologic expertise in earlier studies, the authors themselves employ questionable analytic techniques and epidemiologic reasoning on numerous occasions, and conclude that asbestos miners in Quebec do not have higher death rates from lung cancer than expected, and further that the mortality rate does not increase with increasing length or severity of exposure.

Selikoff [119], concerned that most studies do not differentiate between the different types of asbestos, such as chrysolite, crocidolite, anthophyllite, and amosite, identified all workers in an unnamed company who started work between 1941, when production began, and 1945. From a review with plant management, from product samples, and from workmen's old respirator filters, it was ascertained that only amosite was used in this particular plant, which continued production until 1954. In all, 868 or 93 per cent of the original group was traced, and expected deaths for the period 1960-71 were determined. Selikoff calculated

2.4 expected deaths from lung cancer, while 25 were observed, although smoking histories, since unavailable, were disregarded.

Meurman, et al. [114] studied anthophyllite miners in Finland who had worked in one of two mines for three months or more between 1936-67, with the roster supplied by the company. Location and follow-up of subjects was accomplished by use of the Finnish national population registry and the detailed records of the state church. Follow-up was complete for 95 per cent of the more than 1000 employees who met the inclusion criteria. Interestingly, a comparison group was selected from a nearby nonmining and nonindustrial town, and every asbestos miner was matched with a control for date of birth, sex, and date of death, if the miner was deceased. In addition, a questionnaire was sent to each miner and control, soliciting information on current health status, smoking habits, and the duration, quality, and intensity of work in a dusty environment, as well as age at first exposure. In all, there were 248 deaths, with cases exhibiting a lung cancer excess compared with controls, while digestive system cancers were found in equal frequency in the two groups.

McDonald [115], in a large study, investigated the mortality experience of chrysolite miners in Quebec. Records were collected from 44 companies listing all current and previous employees as of 1966. Approximately 28,000 miners were identified, a quarter of whom were employed as of 1966. Detailed work histories, including more than 13,000 different jobs, were collected. This number was reduced to just under 6000 and, for each of these, and for every year of operation, average dust exposures were assessed on a 13-point scale, based partly on environmental measures conducted since the late 1940's and, for

levels prior to that date, based on interviews with employees of long standing.

Of the original 28,000 members, a cohort of about 12,000 was selected, comprised of persons born between 1891-1920, provided that they had been employed for at least one month, and a detailed search was conducted for all lung cancer deaths among this group. Observed and expected mortality rates were calculated and, in the highest dust category, in which were found 5 per cent of all subjects, the age-standardized mortality rate was 20 per cent higher than in other groups. In addition, the difference in respiratory cancer mortality rates between individuals with minimal and maximal dust exposure was five-fold.

Lung cancer is not the only malignancy associated with asbestos exposure. In two separate hospital-based case-control studies [116, 117], neither of which can properly be called an industrial study since they were not conducted within specific industries, but both of which are quite interesting, a relationship between asbestos exposure and laryngeal cancer has been indicated. The first was conducted in England on 100 consecutive laryngeal cases matched with non-malignant controls, where it was found that 31 per cent of the cases, and only 3 per cent of the controls, reported industrial asbestos exposure, with an average of 27 years exposure.

The second included 43 cases in Canada, each matched with one control for age, sex, and residence within metropolitan Toronto. From personal interviews, occupational exposures to a number of environmental agents, including asbestos, were determined, and smoking histories were obtained. Among the cases, ten had prior industrial exposure to asbestos, while none of the controls reported similar exposure. The mean latent period

was 28.2 years (range = 1-55), although these estimates are based on rather small numbers. An interesting finding was that among men exposed at a younger age, the latent period was longer, although this is not discussed in any detail. The two studies, therefore, report similar findings regarding latency period, and the proportion of all cases with an industrial asbestos exposure (approximately 25 per cent) which seems highly significant, especially if replicated in other, large studies which utilize more detailed work histories.

Uranium Miners

Lorenz [118], in a 1944 paper, summarizes the history of the elucidation of an association between uranium mining and pulmonary diseases. Among miners at Schneeberg (Germany) and Joachimsthal (Czechoslovakia), in the Erzgebirge or Ote Mountain region between Saxony and Bohemia, an ailment called "mountain disease" or Bergkrankheit was described as early as the sixteenth century. In 1913, a German investigator, using a proportional mortality approach, reported that malignancies of the lung accounted for approximately 40 per cent of all deaths among miners in this region. He further stated that during the period 1875-1912, there had been among this group of miners 276 deaths from lung cancer, 64 from tuberculosis, 119 from other lung diseases, and 206 from other causes. Over the years, investigators in this region continued reporting proportional mortality lung cancer rates of 40-70 per cent among miners.

Included in this fine paper are a summary of the physical findings regarding radium exposure in the mines, a review of the data, up to that point, from animal exposure studies, as well as a rather depressing

description of the stark conditions in which the miners worked and lived. In addition, a summary is presented of the different etiologies to which the excess lung disease was attributed over the years, including fungi, mud, and dust containing arsenic, cobalt, and silica. Radon was first suggested as an etiologic agent in 1924.

Archer [119] describes the initiation of studies of uranium miners in 1950, based on the knowledge that uranium and its decay products (radon daughters) are toxic, and based on the evidence from Schneeberg and Joachimsthal cited above. Health examinations were initiated in 1950 and continued through 1960 and included a physical exam and laboratory procedures, as well as obtainment of an occupational history and pertinent social data. Preliminary analysis indicated twice as many observed as expected cases of lung cancer, although based on very small numbers (5 expected), as well as an excess cardiovascular disease and accident rate.

In a rather large study of underground metal miners, Wagoner, et al. [120] selected miners who had completed at least 15 years of employment between 1937-48. The year 1937 was chosen as the initial date because the Social Security System was then inaugurated, and it was used as a source of follow-up information. Mortality analyses were performed through 1959.

Of the 75,000 employee company records reviewed, 1759 miners met the study criteria. Because of discontinuous work patterns, estimates of the number of years of exposure were based on the number of underground shifts worked and, for analytical purposes, the number of person-years of exposure was used. Follow-up was accomplished through the use of insurance records, state vital statistics departments, company retirement programs, and social security records.

In all, death certificates for 930 miners reported to have died during the study period were obtained. All other members of the cohort were assumed to be alive, a procedure which makes conservative the estimates of excess mortality. Overall mortality and cause-of-death distributions among miners were compared with similar findings in the state in which the miners worked, although the name of the company and its location were not divulged. In this manner, expected number of deaths for each cause and calendar year were calculated.

The study population was divided into two groups, Cohorts I and II, as follows: those in Cohort I must have completed at least their fifteenth year of underground mining before 1/1/37 and must have been alive as of that date; members of Cohort II completed their fifteenth year between 1/1/37 and 12/31/48. These groups were created to determine whether "survivorship bias" existed among the members of Cohort I "as would happen if the men who met the fifteen year requirement before January 1, 1937, and survived to enter the study were hardier than those who completed their fifteenth year at a later date".

Age-cause-specific mortality ratios were computed separately for each cohort, and excess was essentially limited to diseases of the heart and lungs. The excess in lung cancer (SMR = 300) was not attributed to excess cigarette smoking among underground metal miners, on the assumption that their smoking histories would not differ substantially from the histories of uranium miners, among whom lung cancer mortality was increased only 10 per cent due to smoking habits. Nativity effects were controlled by separate analyses for both foreign and native-born, and the resultant SMRs were elevated in both groups, although the excess was greater among native-born.

Autopsies had been performed on 15 per cent of the subjects who died, according to death certificates, and verification by either pathological or radiographic examination was available for 73 per cent of the deaths. Since these figures compare favorably with autopsy and verification rates among similar groups from the general population, the lung cancer excess is not ascribed to differences in death certification.

An examination of the data presented in this paper indicates that, on the average, employment within each of the two cohorts lasted 15 years (25,033 person-years of exposure for 1759 persons), although one must wonder why there were not more person-years of exposure, since 15 years was the minimum inclusion criterion. Also, while the authors postulate radioactive "inhalants" as being of possible etiologic importance, no measure of their prevalence within the industry are reported.

Wagoner, et al. [121] conducted a major study of uranium miners in the Colorado plateau with the intention of conclusively demonstrating that the excess lung cancer among uranium miners is due to airborne radiation, an association which was demonstrated by Archer in 1962.

The pool of available subjects came from 5370 miners in the Colorado Plateau, a group which was the basis for numerous additional studies soon to be described. Of this group, 3415 white uranium miners had earlier volunteered for a physical examination, and there was sufficient social and occupational data available for these miners. Follow-up was based on continuing physical examinations, annual company censuses, questionnaires, newspaper clippings, employment offices, vital statistics bureaus, and the Veterans and Social Security Administrations.

Follow-up was 95 per cent complete as of the 1963 cut-off date, with all those of unknown status conservatively considered to be alive. Information from death certificates, autopsy reports, and hospital and physician reports was used by two investigators to arrive at independent diagnoses for the 249 certified deaths among this group of miners.

Expected numbers of deaths for the group under study were computed from age-race-cause-specific mortality rates for whites within the same states as the cases, and total expected deaths were calculated for the period 1950-63. An SMR of nearly 400 (22 observed and 5.7 expected) was determined for malignant neoplasms of the respiratory system:

The investigators capitalized on nearly 12,000 radon daughter (the expected carcinogenic agent) measurements made during the period under study by federal and state agencies. When multiple measures for a given calendar year were available, an average was used, while measures for adjoining years were used when data were not available. These estimates were used to place each subject into one of six cumulative exposure categories, and this was followed by an indirect age adjustment. The analysis indicated that the standardized incidence, per 10,000, increased from 3 to 116 as the cumulative exposure increased.

The reader should be cautious about selective factors in this study, which may either invalidate or strengthen the conclusions drawn. The 3415 miners included in this study are drawn from the 5270 miners in the Colorado Plateau who volunteered for at least one physical, and for whom sufficient data were available. In another report on this group [122], to be reviewed next, it was claimed that by 1960, 90 per cent of all miners in this area had presented themselves for a health examination, although this estimate has not been unequivocally verified.

In the absence of verification, it must be concluded that no well-defined cohort has been established, which means that a precise denominator does not exist, and SMR calculations are therefore questionable. Also, the authors state that members of the study group worked in 1200 different mines during the period under study. Despite these objections, the selective factors, if any, may well have resulted in an under-estimation of mortality from lung cancer, which would serve to strengthen the findings reported.

Using the same group described above, Wagoner et al. [122] stratified the 5370 eligible miners into one of five cohorts, according to uranium exposure - non-white uranium miners and millers, white millers, white miners (surface and underground), among whom 317 deaths were observed during the study period. Among white underground miners, an SMR of approximately 400 for respiratory cancer was calculated. In addition, workers were further categorized, according to duration of underground mining, into one of two groups: 1-4 years and 5 or more years. Among the latter, the respiratory cancer SMR was 1000 (11 observed and 1.1 expected):

This same group of miners within a 15 county region of the Colorado plateau was used by Saccomanno [123] for a lung cancer study which utilized a case-case matching scheme. Cases were divided into one of three groups: 51 uranium miners who had mined for one week or longer and had lived in any of the counties, 121 cases among all other male residents of the 15 counties, and 37 transients who had either received medical care or who had died in the Colorado Plateau. The 51 cases

among uranium miners were further stratified into one of three levels of cumulative radon daughter exposure. The matched analysis indicated that miners got the disease at a younger age than non-miners, that there was an excess of small cell tumor types (oat, round, and polygonal cells) - 57 per cent among miners against 16 per cent among the other cases, and that the proportion of small cell malignancy types increased as cumulative exposure increased. Archer [124] used the data from this study and others and had the cases reviewed by a qualified three man panel. They found that epidermoid and small cell undifferentiated carcinomas, as well as adenocarcinomas, were all found in excess among uranium miners, with small cell carcinomas the predominant type and the only one which was significantly elevated in all cumulative exposure categories. They also concluded, however, that the relative frequency of histologic types is dose-independent, a conclusion which disagrees with the earlier report.

Archer et al. [125] again used Colorado Plateau miners for an updated analysis in 1973, which includes 3366 white and 780 non-white miners of the original 5370, who are said to represent approximately 90 per cent of all miners in the area under study. Miners included in this study had at least one month of underground employment prior to 1964, with 99 per cent follow-up, and mortality analyses for the period 1950-68, during which period there were 437 observed deaths against 277 expected. The investigators then looked at respiratory cancer SMRs separately according to cumulative exposure (7 categories) and "years after start of underground mining" (6 categories) when the cases developed. There was no excess in the lowest exposure category, a significant excess in the next three exposure categories, and an

increasing ratio of observed to expected in the two higher exposure categories. These relationships prevailed across all "years after" categories.

A life-table analysis was used to quantitatively relate person-months of exposure to observed lung cancer occurrence, although the authors admit that there may be distortion, in the same direction, from two sources. First, miners worked throughout most of the study, and therefore most of the latent period, which means that if a miner developed cancer while in the highest accumulated exposure category, most of his person-months of experience would have been in the lower categories. Second, most men in the lower exposure categories started mining more recently than those who contributed most to the higher categories, leading to less elapsed latency time for person-months in the lower exposure groups. Both distortions tend to maximize incidence in the higher accumulated exposure categories, especially when assuming a long latency period. In which case the life-table approach is not ideal. Accordingly, adjustments had to be made for latency period, age, and dose-rate effect, for which two approaches were used: the calculation of observed and expected rates for five-year intervals "after start" of uranium mining, which controls for latency period; and use of a model which makes adjustments for time after the radon daughter exposure within each year.

SUMMARY OF OCCUPATIONAL STUDY DESIGNS

It would be useful, at this point, to summarize the different methods and procedures utilized in the occupational studies reviewed in the previous chapter, and to briefly comment on some of the benefits and drawbacks encountered in their use.

Study Designs and Measures of Effect

A cohort design is generally most desirable for epidemiologic studies since this design allows for a direct determination of the risk-ratio based on a true population at risk. In occupational studies, it is almost always necessary to utilize the retrospective cohort design because of the long latency periods of chronic diseases, although at present there is much activity, among industrial epidemiologists, to initiate true prospective studies, which would naturally involve surveillance. Notwithstanding the benefits of a cohort design, a problem is often encountered in exposure allocation--that is, how does one determine the exposure category to which a subject should be assigned? In non-occupational studies, it is generally rather straightforward, since the choices are often dichotomous--exposed or non-exposed, as, for instance, smoker or non-smoker. The occupational milieu, however, often necessitates a judgemental determination of exposure status. For example, the steelworker study utilized the reductionist approach, condensing 14,000 jobs to 75 subgroups, and further into 10 basic groups.

Workers, however, have a tendency to be very mobile within industries, which means that they have often spent time in many different jobs with diverse exposures.

The steelworker study, additionally, generally required that a worker have a minimum of five years of exposure within an OT (sub-group) before he was assigned to that exposure group. The experiences of this group were then compared with the experiences of a comparison (non-exposed) group chosen from within the industry. The trouble with this approach is that the individual assigned to the high risk OT has almost always worked in other OTs as well, and is therefore not truly unexposed to the hazards of these other work areas. He may even have worked for a number of years in the referent OT, with which his experiences are being compared. While this would tend to conservatize the measures of effect and might therefore be dismissed as only strengthening faith in our conclusions, we must be concerned with the possibility that this "contamination" may mask smaller differences which would otherwise be uncovered.

These methods, then are very similar to the use, within the rubber study, of the most representative OT, which classifies a worker into the OT in which he spent the greatest amount of time during his employment within the industry. Unfortunately, this similarity results in similar drawbacks as well, and should be interpreted cautiously. Additionally, when using the retrospective design one should be very careful to avoid differential outcome bias--among steelworkers, for instance, it was found that the employers were unaware of 43% of deaths from malignancies and only 21% of heart and circulatory disease deaths. Naturally, these differences could cause havoc with even the best designed studies.

The use of the cohort design, whether retrospective or prospective, requires the very careful enumeration of the population-at-risk (PAR), which is generally a highly expensive and difficult task. As an alternative, the case-control design can be used without PAR determination, although the investigator must be very concerned with bias in case identification. In a hospital based industrial exposure case-control study, for instance, such as the laryngeal cancer studies (116,117) among asbestos workers, the researchers must take great care to make certain that cases of a certain type do not systematically seek care at a specialized hospital and thereby avoid the scrutiny of the investigators. When time, money, and extreme rarity of the disease are important considerations, this design is often the one of choice.

We come now to the ambidirectional design, which is the one utilized in the present investigation of stomach cancer, but which was not used in any of the three industrial studies described in this chapter. The ambidirectional design involves the identification, enumeration, and follow-up, in this case accomplished retrospectively, of a cohort of individuals, for whom estimates of risk of various diseases are determined. When an excess risk is identified, it is followed by a case-control study to determine the specific exposures responsible for the excess. Since this design is based only on a comparison of the experiences of the cases and referents, and does not require detailed histories of all other unaffected members of the cohort, it serves to economize exposure determinations, although the necessity for exhaustive cohort identification remains. The present study is not a truly ambidirectional study, however, but should more properly be described as a hybrid design. Had we utilized a true prospective cohort design, the term ambidirectional would have been rigorously appropriate.

Aside from these semantic considerations, a number of additional comments should be made. The study, in this review, most comparable to ours is the steelworker study, because of the diversity of jobs within the industry. In that study, the ambidirectional approach has not yet been used because of the manner in which excess risks were initially identified. While the rubber study first determined overall excess risks for specific diseases, the steelworkers investigators determined these risks for specific OTs. Once having identified a risk, they then followed with a retrospective cohort design which compared the exposed (members of the high risk OT) with a carefully chosen unexposed (another OT) group, while we must follow with a case-control study since the data necessary for the steelworkers' approach has not been collected.

In all designs discussed, a referent group must be chosen for purposes of comparison. Generally, an attempt is made to choose a comparison group from within the industry under study, to avoid any unforeseen differences or exposures, and to avoid problems of the 'healthy worker' type which will be momentarily discussed. In most of the cohort studies cited, the referent was another OT deemed to be unexposed for the hypothesis under consideration, although this is by no means always the case. For instance, in one of the asbestos studies (114) a matched control group was chosen from a nearby non-mining town, while the two laryngeal case-control studies (116, 117) utilized hospital controls.

The appropriateness of the referent group is not only important in analytic studies but may be of even greater significance in the initial descriptive studies on which the analytic investigations are based. As mentioned earlier, occupational studies generally begin with an assessment

of risk in the general industrial population, or in some large sub-groups within this population, most often by use of the standardized mortality ratios (SMRs) or standardized proportionate mortality ratios (SPMRs), both of which require a referent or standard population.

Since the SMR is an indirect standardization, age-specific (if we are dealing with an age standardization) disease rates for some "standard" are needed for the calculation of expected numbers of deaths. Usually the most precise available estimates of these rates are for the general U. S. population, and, because of their accuracy and availability, are often used. The problems which the use of these non-industrial referents engender are well known and referred to as the healthy worker effect. Briefly, use of disease rates from these groups often leads to an underestimation of the SMR because an employed population, by virtue of being employed, is healthier than the general population, which includes disabled and hospitalized people. Therefore, the observed disease frequency is lower, and the expected frequency is higher, in a relative sense, and this often leads to low SMRs. If the SMR is underestimated, however, important disease excesses may be missed entirely. Ideally, disease rates should be derived from other industrial populations which are free from the exposure under consideration. Use of a referent of this nature would make the identification of a specific disease excess, within the unique population under study, more probable. In the absence of a disease rates for a suitable industrial referent population, however, general populations are used instead and are quite suitable as long as the investigator is aware of their limitations.

When enumeration of the PAR is not possible, the SPMR is often used to provide some evidence of disease excess. The well-known limitation of the SPMR, however, is that it indicates a relative, and not absolute, excess, and can therefore be quite misleading. Despite these drawbacks, however, there are instances where a cause-specific proportional mortality ratio is so clearly elevated, as in the early uranium miner studies (118), that concern about this limitation would not be appropriate.

Confounding and Effect Modification

Epidemiologists are always concerned about the role of confounders in the estimate of effect, especially when dealing with known confounders. These known confounders are controlled either during subject selection or data analysis, and the methods used for control of confounding in occupational studies do not differ, at least in this literature review, from methods generally used in other studies.

The confounders most commonly encountered are age, race, sex, date of initial employment and total duration of employment, which were all of importance in the present study as well. The methods used for control of these confounders, in the studies reviewed here, include matching during subject selection and stratification in the analysis. In addition, there are available a number of multivariate statistical techniques which allow for the separation of the effects of confounders and true risk factors, among which is Miettinen's confounder summarization score.

In the studies reviewed here, matching was used in both cohort and case-control studies. The intent of matching is to make the subjects as nearly alike as possible for extraneous factors so that any differences between subjects (cases and controls or exposed and non-exposed) will be

explained by the putative etiologic factors under investigation. The major limitation of course, is that once the investigator has matched on a factor, the effects of that factor can no longer be determined, although by its nature of being a confounder, the interest of the investigator is not focused on that factor anyway.

The other method used to control confounding was to stratify in the analysis without having matched during subject selection, although it should be here pointed out that even when matching has been performed, stratification in the analysis is still used. When stratification without matching is used, the idea is to determine the effect of the variables under study within narrow ranges of the known confounders, so that these confounders cannot have much of an impact on the measure of effect. This method of stratification in the analysis was quite commonly used in the studies reviewed here.

In only one study, where the combined effects of smoking and asbestos exposure in neoplasia were examined, did the investigators look for interactive relationships or effect modification, the latter being defined as the non-uniform association between exposure and disease across different categories of the modifier, a term which is sometimes used interchangeably with interaction. Selikoff and associates (126) report the experiences of 370 men who were alive as of 1963, 94 of whom had died during the next four years, and for whom there were available accurate smoking and asbestos exposure histories. Of the 370 men under investigation, 283 had smoked cigarettes regularly at some time.

Using a lifetable approach, based on the U. S. general white male age-specific death rates, for the calculation of expected numbers of deaths, it was determined that only 47.5 deaths were expected, compared

with the 94 that were observed. Furthermore, the excess deaths were due to bronchogenic carcinoma, mesothelioma of the pleura and peritoneum, asbestosis, and cancer of the stomach, colon, and rectum. The authors then calculated the expected number of deaths that would have occurred among this group of 370 men if their lung cancer mortality experience did not differ from other men, taking both age and smoking habits into consideration. The investigators found 24 deaths from bronchogenic carcinoma in this group, while only 3.16 were expected, a ratio of approximately 8 to 1, although they found no bronchogenic cancer deaths among men in this group who had never smoked regularly, or who had only smoked cigars or pipes, leading the authors to conclude that asbestos dust exposure, without concomitant smoking, does not increase the risk of bronchogenic carcinoma. The authors further calculated that only 0.26 workers who had regularly smoked would have been expected to die of bronchogenic carcinoma, during the period under study, if they had neither smoked nor been occupationally exposed to asbestos dust, while there were actually 24 deaths due to this cause. This is the really startling conclusion--the interactive effect of both smoking and asbestos exposure results in a nearly one hundred-fold risk of dying from bronchogenic cancer compared with men who were not exposed to either. This finding is an excellent illustration of the importance of searching for interaction when there are additional known risk factors and when the appropriate data are available.

Exposure and Latency

There is an attempt, in most occupational studies, to estimate exposure qualitatively and quantitatively, so that some determination

of the relationship between exposure characteristics and disease occurrence is possible.

Generally, an initial minimal exposure duration, in years, is necessary for inclusion in the "exposed" group. For instance, a minimal five-year exposure was necessary in most of the steelworker analyses, while a minimum of 15 years of employment was necessary for inclusion in one of the uranium studies (120). After the inclusion criteria had been set, however, there was then additional classification into categories of total duration, in years or months. This procedure was used in studies of all three occupational groups reported here. Additionally, in one of the steelworker studies involving crane men (103), there was an attempt to qualitatively determine the type of exposure (gaseous, particulate, or clean) with which duration was correlated.

In two of the asbestos studies cited (112,115), there was some determination of dust levels. In the first, dustiness was assigned to one of three levels which were assumed to be interval data, with level three having 3 times as much dust as level one. In the second, average dust exposures were assessed on a 13-point scale, based on both environmental measures and on interviews with knowledgeable employees. Observed and expected mortality rates were then determined for each of the dustiness levels.

In addition to independent correlations between disease occurrence and duration or type of exposure, these two characteristics are often combined, such as in the asbestos study (112) with three dustiness levels, where a weighted exposure average, based on these levels and on total duration, was used.

The most extensive determinations of exposure were made for the uranium studies (127), where working levels (WL) and working level

months (WLM) were used. The working level is a measure of concentration, specifying an amount of radon daughters in a liter of air releasing a specified amount of potential alpha energy. After the determination of the WL had been made, the investigators then calculated the working level months. These WLMs represent the cumulative product of the length of underground exposure in working months (170 hours) and the concentration of radon daughters in working levels (WL) for specified mines and calendar years.

In most studies where latency period was examined, it was calculated as elapsed time between first exposure and death. Death was used as the endpoint because mortality data were generally used, although these latency estimates can be rather misleading for diseases with long survival times or low case-fatality rates. Since lung cancer, however, was the major type of malignancy under investigation in these studies, these two limitations were probably not of major importance. When latency was presented in a straightforward manner, it was generally reported as a simple mean and range. In one study (125), however, latency period, in terms of years after the start of underground mining when the case developed, was cross-classified with cumulative exposures for a total of 42 categories in which were found an increasing ratio of observed to expected deaths in the two highest exposure categories, a relationship which prevailed across all "years after" categories.

Summary

A careful analysis of the studies cited above, which are felt to be representative of generally good occupational studies, reveals that there are certain basic characteristics of properly conducted investigations in this field.

First, and most important, is the careful definition and delineation of the cohort, on which all subsequent determinations of excesses or deficits of disease occurrence will be based, and from which generally are drawn all cases of a specific disease for retrospective, such as case-control, studies. SMRs are consistently used for comparisons of observed and expected numbers of cases, although the referent group varies from study to study, and includes rates derived either from the U. S. general population, from the geographic area nearest the site of investigation, from within the study population, or from comparable industrial groups with similar work characteristics but without the exposure under investigation.

When possible, precise types of exposure are determined (e.g. particulate vs. gaseous), preferably verified by environmental sampling. Almost always, disease rates are correlated with an estimate of duration of exposure, an estimate which depends on availability of data and often takes the form of years or person-years of exposure to the agent under study. Work experience is generally further categorized into different levels of intensity of exposure, often based on retrospective questionnaires. Mean latency periods are also generally presented, and they are usually based on elapsed time from first exposure. When data are available, occupational disease occurrences are compared across different geographic areas and across plants. It should be remembered, however, that estimates of exposure are quite complicated when there exists more than one putative etiologic agent, as is the case in the steel and rubber industries, but which is apparently not a problem in the uranium miner and asbestos worker studies.

Wagoner (121) has summarized the types of evidence needed to reasonably infer causality from an occupational study, while at the

same time advocating the use of retrospective work histories and exposure data for the identification of occupational etiologic agents.

The steps are:

- 1) demonstration of an excess risk
- 2) demonstration of a dose-response relationship
- 3) persistence of both 1. and 2. when known confounders are eliminated
- 4) establishment of the consistency of the association
- 5) establishment of the specificity of the association
- 6) description of the histologically distinctive distribution of the disease, especially among malignancies, when possible, according to site and type

But even when all of these criteria have been satisfied, associative conclusion should be made with great caution, for, as Donaldson (128) says:

epidemiologic studies can reveal the existence of a health hazard, can define its distribution and dimensions in the population, can identify associations which may be suggestive of etiology, and can provide estimates of levels of risk under varying conditions. Epidemiologic data will not - and should not be expected to - provide incontrovertible proof of a cause-effect relationship. This fact, however, makes neither the epidemiologic method, nor the data derived therefrom, any less scientific.

MATERIALS AND METHODS

Cohort Description

All but three of the cases, and all controls, were selected from the ten year cohorts which were reconstructed for two companies' plants in Akron, Ohio. These cohorts were retrospectively identified, in very similar fashion, at both companies, and include all hourly (factory) active and retired employees who were 40-84 years of age as of 1 January 1964. The cohorts, or populations at risk, were followed for the ten year period 1964-73, and death certificates for almost all deaths among members of these cohorts were collected. At Company A, the cohort numbered 6678 while at Company B, the population at risk numbered 10,655.

These cohorts were enumerated on the basis of a very thorough check of both management and union records and included a search of both payroll and pension records, death claims, severance awards, and employment exits and transfers. Deaths among cohort members were identified mainly from life insurance death claims, but were cross-checked both internally against company records and externally with the U. S. Internal Revenue Service. Because of the company financed life insurance policy, to which hourly employees are entitled after ten years of service, follow-up is approximately 97% complete for each of the two companies. In all, during the ten year period under observation there were 1983 deaths at Company A and 2508 at Company B.

Case Selection

Nearly all of the approximately 500 subjects in this study were chosen from the cohorts just described, with the exception of three cases which occurred during 1974 or 1975. Before this present study was undertaken, standardized mortality ratios, based entirely on the cohorts described above and using the age-sex-specific stomach cancer rates from the 1968 U. S. general population, were determined after completion of nine years of the ten year period under study, and we calculated an SMR of 187 at Company A and 123 at Company B for the full age range 40-84, the former including both white and black males, while the latter examined the experience of white males only. To correct for an all-causes SMR of under 100 among the group under study, the stomach cancer SMR was divided by the all-causes SMR (Table 1) to arrive at adjusted stomach cancer SMR, which was 189 at Company A and 131 at Company B. Additionally, since there was some objection to the use of 1968 U. S. national data for the calculation of SMRs during a relatively long ten year period, stomach cancer SMRs were calculated separately for the five year periods 1964-68 and 1969-73, using national data from the midpoints of these quinquennial periods, from which we derived SMR estimates which did not differ appreciably from these estimates already presented.

In this manner, we established the existence of an "excess" of deaths, in contrast with an age-race-sex comparable group, from gastric malignancies, based on nosologized death certificate analysis, within the rubber industry and we decided to conduct the present investigation to determine in which manner, if any, the work histories and other appropriate attributes of cases of stomach cancer differed from matched controls. As mentioned above, however, case selection was expanded to include those which occurred in 1974 and 1975, as well as those which were identified during the interval 1964-73.

Despite the two year extension for case inclusion, all controls were nonetheless limited to the initial ten year period under investigation, reasoning that since the controls were to be matched, on numerous factors, with the cases, the restriction of controls to the ten year interval would not in any way bias our conclusions, so long as properly matched controls could be found for each case. In addition, death certificates for all controls through 1974 were checked to make certain that none of the controls had died from stomach cancer.

We examined the death certificates which arrived at OHSG and defined a case of stomach cancer as anyone whose death certificate anywhere included a diagnosis of stomach cancer, either as an underlying or contributory cause of death (50), or when listed in the "other significant conditions" (6) section or as immediate cause (34). Initially, 50 cases were identified among Company B employees and 54 among those who worked at Company A, based on computer printouts requesting a listing of all individuals who had an ICDA code of 151.9 anywhere on the death certificate. During a subsequent search of existing death certificate files for the two companies, only 46 of the 50 (92%) of the Company B, and 44 of the 54 (81%) Company A, death certificates were located, the others presumably being lost, although our computerized records indicated the presence of stomach cancer somewhere on lost death certificates. For the available death certificates, Table 14 presents the place where the listing was found and Table 15 summarizes the terminology used to describe the cancer and the frequency of each type, according to information abstracted from the death certificates.

An examination of these records indicated that one of the Company A cases was a "carcinoma of duodeum" and this was subsequently confirmed by tumor registry data, while among Company B cases we found one listed as "large bowel carcinoma with metastasis (linitis plastica)", and another

TABLE 14

PLACE ON DEATH CERTIFICATE WHERE STOMACH CANCER WAS LISTED

<u>PLACE</u>	<u>NUMBER</u>	<u>PER CENT</u>
A (Immediate Cause)	34	38
B (Underlying Cause)	31	34
C (Underlying Cause)	19	21
D (Other Significant Conditions)	<u>6</u>	<u>7</u> -
TOTAL	90	100

TABLE 15

TERMINOLOGY USED TO DESCRIBE THE STOMACH CANCER PRIMARY

<u>TERMINOLOGY</u>	<u>NUMBER</u>
Carcinoma	67
Adenocarcinoma	17
Signet Cell Adenocarcinoma	1
Esophageal & Gastric Carcinoma	1
Mesenchymal Tumor (Stomach)	1
Gastric Ulcer (Cancer)	1
Lymphosarcoma of Stomach	1
Large Bowel Carcinoma with Metastases (linitis plastica)	<u>1</u>
TOTAL	90

as "esophageal and gastric carcinoma", and one listed as "gastric ulcer (cancer)" with no confirmatory tumor registry information available for any of these. The first of these four was excluded while the remaining three were included as unconfirmed cases. It should be immediately noted that all "cases" were eliminated from the case pool when there was evidence, from either death certificates or tumor registries, that the primary was at a site other than the stomach.

Tumor Registry Confirmation

As just described the selection of cases was based on a computerized listing of all cohort members who had an ICDA code 151.9 listed on their death certificate, in addition to the few cases identified from 1974-75 deaths. This list was then checked against the records of the four largest hospitals in the Akron area: Akron City, Akron General, St. Thomas, and the Barberton hospitals. The first three had hospital-based tumor registries, while the last did not. Each hospital searched for the records of all of the 105 "cases" on the list and this author personally abstracted the pertinent information at all hospitals except Akron City, where the tumor registrar performed this task. The information abstracted included the following when available: date and method of diagnosis, histological (pathological) description, site of tumor within the stomach. In all, hospital records were found for 76 (72%) of the 105 subjects, and either all or some of the desired information was obtained, although it should be noted that the acquisition of the record does not necessarily mean that a definitive diagnosis was made, as for instance some records which indicated carcinoma (NOS) of the stomach based only on a clinical impression, which does not differ much from an unvalidated opinion which might be found on some death certificate.

At the Barberton Hospital, which was the only one of the four without a hospital-based tumor registry, this author examined the entire hospital record, from which was abstracted the desired information. At Akron General and St. Thomas, the abstract prepared by the tumor registrar was used as a basis for information collection, although these abstracts often did not include the site of the tumor within the stomach, which was instead determined by an examination of surgical and/or radiological reports, when possible. This investigator was not allowed personal access to the records at Akron City, where the data were compiled by the tumor registrar, and although requested, the site within the stomach is often missing because the registrar apparently limited herself to information on the registry abstract, which generally does not request identification concerning the specific site within the organ with the primary. When available, however, it was included.

Based on all the diagnostic information collected, a four digit code was constructed and assigned to each case, with the following information included: method of diagnosis, histologic type, site within stomach, and death certificate diagnosis. Table 16 is included to indicate the range of values for each of the four variables, and these codes will be used during analysis to differentiate between definite and possible cases, the former including those confirmed anywhere in the hospital record.

Control Selection

Control selection at both Company A and Company B was conceptually similar. As discussed earlier in the description of the design, two sets of controls, with two subjects in each set, were selected for each case. The first set was matched with the case on three factors: age as determined by year of birth and age at death (each within three years), race, and sex.

TABLE 16

CODING SCHEME FOR THE FOUR DIGIT PATHOLOGY CODE

<u>DIGIT I</u>			<u>DIGIT II</u>		
<u>METHOD OF DIAGNOSIS</u>			<u>HISTOLOGY</u>		
<u>CODE</u>	<u>MEANING</u>	<u>NO.</u>	<u>CODE</u>	<u>MEANING</u>	<u>NO.</u>
1	Histology		1	Adenoca-NOS	
2	Radiology		2	Adenoca (undiff. or poorly diff.)	
3	Autopsy		3	Adenoca (well diff)	
4	Clinical		4	Carcinoma/Cancer	
5	Surgery		5	Other	
8	NA		8	NA	
9	UNK		9	UNK	

<u>DIGIT III</u>			<u>DIGIT IV</u>		
<u>SITE WITHIN STOMACH</u>			<u>DEATH CERTIFICATE DIAGNOSIS</u>		
<u>CODE</u>	<u>MEANING</u>	<u>NO.</u>	<u>CODE</u>	<u>MEANING</u>	<u>NO.</u>
1	Cardia & Fundus (upper third)		1	Stomach Cancer mentioned	
2	Body (mid third)		8	NA - Other Primary	
3	Pyloric region (lower third)		9	UNK	
4	Other Combination				
8	NA				
9	UNK				

This group will be referred to as the ARS group. The second group of two controls, to be called the ARSD group, was matched on duration of employment, within three years, in addition to the three factors on which the first group were matched. It was also stipulated, for the four controls of a given case, that if the case was deceased the controls must have achieved at least the same age at death as the case with which they were matched, in addition to the exclusion of any deceased control whose death certificate anywhere indicated a malignancy (ICDA codes 140-239). If the control was alive at the time of selection, naturally, this last stipulation was not applicable, although the possibility exists that the control had, in fact, experienced a non-fatal malignancy of which this investigator would be unaware.

Two notes are appropriate at this time. First, the matching which involved calendar years (year of birth, age at death, and employment duration in years) was executed in disregard of months and days and may therefore result in an actual matching range greater than the stated one. For instance, the birth date of a case may be 1 Jan. 1900, while that of its matched control can be 31 Dec. 1903, resulting in an actual range of four, rather than three, years. Since the maximum difference is therefore four years and the minimum zero, the average difference was probably in the two-year range.

Second, the 'duration' used for matching is an estimate of that variable, based on what is variously referred to as seniority or continuous service date. These dates are determined by the individual companies based on a formula, agreed upon by both union and management, which subtracts from the actual starting date the amount of time spent away from the plant during unexcused, or unrecognized, absences. These

seniority dates are therefore adjusted and not actual starting dates. Because of the great amount of work which would have been necessary to calculate actual duration, which is not already on existing computer files for the PARs under study, this surrogate measure was used instead. This drawback, coupled with the use of calendar years discussed in the preceeding paragraph, can lead to differences in actual duration which are considerably greater than the stated matching criterion of three years. We will examine this during analysis of the actual work histories, to be described in the next chapter.

It should be immediately noted, however, that before the duration match was executed, some preliminary analyses were conducted in one company to determine the difference between the two methods of estimating employment duration. Table 17 presents the frequency distribution between duration determined by subtracting actual date in from date out, and duration calculated by subtracting seniority date from date out. This variable is called DURDIFF and, as can be seen from an examination of the table, the longer the duration of employment, the greater the likelihood of a difference in estimated duration, with an overall agreement rate of 61%.

The decreasing agreement between the two estimates as duration of employment increases may be explained in one of two ways: first, seniority dates were calculated, by management, in a manner which has become, with time, less stringent and more favorable to the employee, and second, the longer one has been employed the greater the opportunity for unexcused leaves of absence.

Not to be lost in this comparison of the two methods of determining duration of employment, however, is the fact that neither is an entirely accurate estimate of time duration. The one which uses seniority data is

TABLE 17

DIFFERENCE IN DURATION (DURDIFF) WHEN CALCULATED
 ACCORDING TO TWO DIFFERENT METHODS^a,
 ACCORDING TO TOTAL EMPLOYMENT DURATION^b

<u>PER CENT OF INSTANCES^a</u> <u>WHERE DURDIFF=0</u>	<u>TOTAL DURATION^b</u>
77.9	10 years
81.5	10-19
79.6	20-29
39.5	30-39
27.6	40 and over
61.0	TOTAL (ALL DURATIONS)

^aDURDIFF = DUR1 - DUR2
 DUR 1 = Date Out - Actual Date In
 DUR 2 = Date Out - Continuous Service Date

^bTotal Duration, for this analysis, is based on DUR 1

dependent on the unique management-union agreements and methods of determination on which it is based, while the estimate which makes use of actual starting date does not subtract from total duration the time the employee was actually away from the job. The analysis of the difference between the two methods, described above, was conducted on the total 1964 Company B cohort, which includes over 13,000 individuals of all race-sex combinations. As noted, the general agreement rate, expressed as agreement within one year, was 61%, although the differences ranged from 1-40 years.

The actual mechanics of control selection differed somewhat at the two companies. At Company B, lists of eligible controls for each subject were generated by computer, from which the appropriate number of controls was randomly selected. At Company A the entire procedure was executed manually, which was a very time consuming process based on a one-liner printout which contains very basic information such as years of birth and hire, social security number, etc. of all individuals who were part of what is variously called the 20% or PAR sample, which is an age-race-sex stratified random sample of the entire 10 year cohort on which the SMRs are based. Control selection was limited to this PAR sample because the detailed work histories for the individuals included in this sample have already been entered on the computer, presumably in a relatively final form although in actuality these work histories require so much editing and correcting that their utility, in present condition, is far from ideal.

Since Company A deficiencies have already been broached, control selection at this company will be described first. As mentioned, a one-liner, which included year of birth and death, race and sex and employment duration based on seniority date for all members of the PAR sample, was the basis of control selection. First, the year of birth of the case was noted and all subjects in the sample whose birth date was within three

years of that of the case, and whose race and sex matched, were blocked off and counted. A table of random numbers was then used to choose randomly two of these eligible controls for the ARS group. Within this same blocked off list, those whose durations fell within three years of that of the case were then ticked off and counted and, once again, a table of random numbers (or dice or a single die, if the number of eligibles was small), was used to randomly select two of these individuals as ARSD controls. Before a subject was finally chosen as a control however, two additional checks were made, as stipulated in the chapter describing our design: if the control was deceased, he must have achieved at least the same age at death as the case with which he was being matched, and he was not eligible if a malignancy of any kind was indicated anywhere on his death certificate. This latter determination was made by an examination of the Company A death certificates which are here at OHSG and which are reasonably up to date through approximately 1975. Only when a control met all of these eligibility requirements was he accepted, and quite a few were rejected because of an unacceptable age at, or cause of, death. Additionally, individuals were eligible as controls for only one case and, once chosen, could not be chosen again. Some individuals were occasionally chosen twice, but these errors were subsequently spotted and corrected. Because of the numerous matching constraints, however, a full complement of controls could not be found for a few of the cases.

The procedure was conceptually similar at Company B, although the initial stage of identification of all eligibles was computerized and the reservoir of eligible controls included the entire 10 year cohort and not just a sample of it. For each case, a printout was obtained which included all ARS eligible controls, while those who were ARSD eligible as well were

so identified. Included in this program were the same restrictions concerning age at, and cause of, death and those individuals who did not meet these criteria were eliminated a priori and did not even appear on the printout. For each case the pages listing eligible controls were numbered and a random number table was used, first to select a page, and then a subject, this procedure being executed twice for the selection of the ARS controls. For ARSD selection, after a page was randomly chosen the number of starred entries on that page was tallied and either dice or a random number table was used for final control selection, this procedure again being twice executed.

As can be seen, therefore, while the mechanics of control selection differed slightly at the two companies, the matching criteria and restrictions were identical, if one accepts as identical the use of either a stratified random sample of a PAR or the entire PAR as a control reservoir. Because of these similarities in case and control selection, as well as the availability of a cross-referenced OT dictionary which transforms company-specific OTs into common or standard ones, the possibility exists for combining strata (a stratum is a case and its controls), when appropriate, during the analysis.

Additional Data Aquisition

Much of the data necessary for this study were not available at OHSG and visits were made to corporate headquarters at both Company A and B in Akron.

As described above, Company A controls were members of the PAR sample, whose detailed work histories had already been entered on the computer and, while the cases were naturally not restricted to this sample, almost all of them were on one file or another at OHSG. In addition,

the raw work histories which Company A sent to OHSO include place of birth, so the combination of these serendipitous factors made the task at Company A headquarters rather simple. Some minor problems were encountered, however, in trying to determine years of education from the work history folder face, which listed only completed years of high school or college. Since original applications were often unavailable, this summary had to suffice, although the interpretation of zero years of high school is moot since one cannot assume that the individual had completed junior high school or elementary or, in fact, that the individual had any education at all.

In addition, the contents of some of the very old personnel envelopes were destroyed after "sometime" and all that was kept was a copy of the folder face, which lists only the first portion of the work history. Also, old pieces of work histories (and indeed there are numerous pieces of work histories scattered throughout the folder), were sometimes so aged that they could not be read or opened without tearing or breaking them. Despite these minor problems, however, data collection proceeded quite smoothly and almost all necessary data were collected.

The problems at Company B corporate headquarters, unfortunately, were more numerous, but most of them were more or less satisfactorily resolved before departure. A brief overview of the record system may prove quite helpful in following this discussion and will therefore be presented first.

Personnel folders of employees who retired prior to 1962 are stored separately from those who retired after this date, the former being stored in the basement at corporate headquarters and not subject to the same care in up-keep as the later retirees. Specifically, misfiling is not uncommon and the aging of the folders themselves often lead to gaps in the work histories, a problem which was encountered at Company A as well. The

folders themselves are arranged in the following manner: the work histories for the period 1911, when the plant was apparently opened, to approximately 1930 were entered on index-sized cards kept in the folder, jobs held between 1930-1962 were entered on the folder face, and those held after 1962 are typed by some apparently computerized system onto special large sheets kept within the folders, and the legibility of these different components differed substantially. Least legible were those on the folder face, since the dates indicating when an employee began a specific job were written at the extreme edge of the folder, which was apparently subject to the greatest wear. In cases where the dates could not be determined, a careful estimate was made and, when no additional evidence was available, the midpoint between the preceding and succeeding dates was used.

The determination of education caused some interesting problems as well. First, there was often more than one employment application within the folder, each of which requested information concerning education in a different manner. In one, the applicant was requested to indicate the number of completed years of education while the other just requested a tick next to either elementary, junior, or senior high school although it is not clear whether the tick indicated completion of that level or just some exposure to it. And even in the latter case if the applicant indicated the completion of one year of high school, is this nine or ten years of education? While on this topic, two additional observations will be related. First, there are very many Company B, Akron employees from the neighboring state of West Virginia and, in fact, Akron is sometimes jocularly referred to as the capital of West Virginia. Curiously, almost every West Virginian indicated eight years of education, almost as if they were instructed to do so. Also, the educational attainments of foreigners are

difficult to determine because over twenty foreign countries are represented and educational equivalents between these countries and the United States, especially as long as 50-75 years ago, are not readily available. This conversion problem was encountered among the foreign-born at Company A as well.

The frequent existence of more than one application form caused problems in the determination of marital status as well, since a number of years separated the two forms, during which time marital status may have, and often did, change. Since not all folders contained more than one application, we used the status reported on the first application for the sake of consistency.

A number of individuals had indicated, in their personnel folders, transfers to salaried positions; sometimes permanently but generally for short periods of time. These are generally all classified as simply "transfer to salary" although it should be noted that if the salaried position was that of a foreman or some similar job, exposures actually continued during this period and we have no knowledge of the specific exposures involved. Additionally, there is no subtraction of time for isolated work stoppages and industry-wide strikes which, although probably involving relatively short time periods, should perhaps be taken into account.

Socio-Economic Status (SES)

Despite the fact that all subjects in this study are blue-collar workers, we were interested to know whether their socio-economic status was similar, especially since this factor has been associated with much of the variation in stomach cancer incidence. In 1949, Company A instituted a system of

identifying each job with a five-digit code which, along with the Department number, uniquely determined each specific job within the plant. Each of these jobs was then evaluated for twelve factors: education, experience, skill, initiative and ingenuity, mental effort, physical effort, responsibility for material, responsibility for equipment, responsibility for safety of others, responsibility for work of others, work conditions, and hazards.

An evaluation of each factor was made for every job, and points were then assigned for each factor according to its importance, the latter based on different weights for each factor. In this manner, a score was determined for each factor, based on which a total score was then calculated by summation of the individual scores. For the purposes of this study, the scores for the first four factors and the total score were used to determine the skill level of the job which in turn was used as a surrogate measure of socio-economic status, on the assumption that the more highly skilled jobs generally pay the highest salaries. Despite the imperfectness of this measure of SES, we felt that along with education we would get a reasonable estimate of differences in the socio-economic status of the subjects in this study.

It should be recalled, however, that this evaluation was initiated in 1949, so a substantial number of subjects had few, if any, evaluated jobs. In addition, some of the five-digit job codes were illegible on the work histories, so even when an evaluation was available we occasionally could not use it, and scores were not always found even when a five-digit code was present. The existence of a similar system at Company B is not well documented.

Comments Concerning Some Variables on File

Occupational Titles (OTs) are categories of jobs based on similar production processes and provide a mechanism for condensing the thousands of jobs within the industry into a manageable number for analytic purposes. Company A uses a four letter OT code and has 110 OTs, while Company B has 119 and uses a three digit code. Because we wished to pool data from both companies for some analyses we needed a uniform OT system, and since there is not a one-to-one correspondence between the OT systems of the two companies, we had to use the Company A system which has fewer OTs. Specific analyses were based either on OTs or OTGs (Occupational Title Groups) which number approximately twenty for standard use. OTGs may, however, be created to reflect specific exposures, a procedure which was used to determine odds ratios for carcinogen-specific OTGs in this investigation. Appendix I contains detailed descriptions of both the OTs and the standard OTGs.

An examination of the file format indicates two calculations involving duration- JOB DURATION and TOTAL DURATION. The former is item specific, indicates the number of days spent in the job which the item represents, and is calculated by subtracting the date into that job from the date out, on the basis of 30.42 days in a month and 365 days per year. For instance, if the dates in and out were 1/1/49 and 3/29/49, the JOB DURATION would be 89 days, from which the reader should notice that weekends, holidays, and other non-work days are included. This was done because we had no readily available way to determine how many real work days were included, especially since week-end work was not uncommon. TOTAL DURATION is simply the sum of JOB DURATIONS expressed in months (based on 30.42 days per month) in active OTs, with durations from the following OTs excluded: salary, inactive, retired, sick, lay off, dead, leave of absence, miscellaneous absence, exit,

disability retirement, and military duty.

One additional variable - AGE AT DEATH - requires comment here. Examination of the file reveals a value for this variable for every subject in the study, even when the date of death = 888888 (not applicable or still alive). For deceased subjects, this variable has literal meaning; when the subject was still alive as of 1/1/76, this variable actually represents the subjects' age on that date, which is the termination date of the study.

Format

An intermediate file, including all available information for this study was created at OHSG. This file was used for data analysis either directly or as the basis for creation of specific files for different types of analyses, the latter including an SPSS file of fixed record length and a special file for the matched case-control analysis. The format of the intermediate file is presented in Table 18 and a list of variables, with appropriate explanations, is shown in Table 19. Tables 20-22 show the coding Formats for marital status, education, and birthplace.

Analysis

SPSS or SAS procedures were used for all statistical analyses reported in this study, with the exception of the matched case-control procedure. The latter computerized procedure was developed at the OHSG and a detailed description of it, along with the algorithm on which it was based, is presented in Appendix II. For the packaged procedures, the algorithms are available in the manuals from which they are derived.

The general format of the analysis is the presentation and discussion of the descriptive findings separately for case and control groups by company. This is followed by a comparison of these findings which include

FORMAT FOR THE INTERMEDIATE STOMACH CANCER FILE

[illegible]

TABLE 19

LIST OF VARIABLES, COLUMN NUMBERS, AND BRIEF EXPLANATION
FOR THE INTERMEDIATE STATION CARDS FILE

Variable	Col.	Explanation
Company number	1	0 = Company A; 1 = Company B
ID number	2-3	Identifies a set (case + 3 & 4 = ARSD controls)
c/c number	4	1 + 2 = ARS controls
Job Code	5-9	5 digit code, started in 1949
SES education score	10-11	
SES experience score	12-13	
SES skill score	14-15	
SES initiation score	16-17	
Total SES score	18-20	
SS #	21-29	
Sex	30	1 = male, 2 = female
Race	31	1 = white, 2 = black
Educ	32	See coding instructions
H Stat	33	See coding instructions
Item #	34-35	A work-history entry
Company A OT	36-39	a 4-letter code
Date In	40-45	for specific item number
Date Out	46-51	for specific item number
Dept #	52-55	for specific item number
Company B OT	56-58	a 4 digit code
Job dur	59-62	duration, in days, in specific item
Birth Date	63-68	
Sen Date	69-64	Seniority or continuous service date
1st date in	75-80	first date employed
Last date out	81-86	last date employed
Death date	87-92	888888 if still alive
UCD	94-97	ICDA code
Birthplace	98-99	See coding format
Pathology Code	100-103	See coding format for cases 7777 for controls
Age at Death	104-105	Age at death or age as of 01/01/76
Total Duration	106-108	In months, for active OTs
Exposure Age	109-110	Age at Hire

TABLE 20

CODING FORMAT FOR MARITAL STATUS

Company A

1 = single

2 = married

3 = separated or divorced

4 = widowed

9 = unknown

Company B

1 = single

2 = married

3 = separated

4 = divorced

5 = widowed

9 = unknown

TABLE 21

CODING FORMAT FOR EDUCATION

Company A

1 = completed grade school (6 years)

Company B

1 = some or all grade school (6 years)

Company A and B

2 = some junior high school (7-8 years)

3 = graduated junior high school (9 years)

4 = some high school (10-11 years)

5 = graduated high school (12 years)

6 = some college or technical school

7 = graduated college

8 = not applicable (no education)

9 = unknown

TABLE 22

CODING FORMAT FOR BIRTHPLACE

01 ALABAMA	37 PENNSYLVANIA
02 ARIZONA	38 RHODE ISLAND
03 ARKANSAS	39 SOUTH CAROLINA
04 CALIFORNIA	40 SOUTH DAKOTA
05 COLORADO	41 TENNESSEE
06 CONNECTICUT	42 TEXAS
07 DELAWARE	43 UTAH
08 DISTRICT OF COLUMBIA	44 VERMONT
09 FLORIDA	45 VIRGINIA
10 GEORGIA	46 WASHINGTON
11 IDAHO	47 WEST VIRGINIA
12 ILLINOIS	48 WISCONSIN
13 INDIANA	49 WYOMING
14 IOWA	50 ALASKA
15 KANSAS	51 HAWAII
16 KENTUCKY	52 ARMENIA
17 LOUISIANA	53 GERMANY
18 MAINE	54 SYRIA
19 MARYLAND	55 ENGLAND-WALES
20 MASSACHUSETTS	56 CZECHOSLOVAKIA
21 MICHIGAN	57 AUSTRIA
22 MINNESOTA	58 ITALY
23 MISSISSIPPI	59 HUNGARY
24 MISSOURI	60 AUSTRO-HUNGARY
25 MONTANA	61 RUSSIA
26 NEBRASKA	62 TURKEY
27 NEVADA	63 YUGOSLAVIA
28 NEW HAMPSHIRE	64 RUMANIA
29 NEW JERSEY	65 POLAND
30 NEW MEXICO	66 W. UKRAINE
31 NEW YORK	67 SCOTLAND
32 NORTH CAROLINA	68 LITHUANIA
33 NORTH DAKOTA	69 IRELAND
34 OHIO	70 SWEDEN
35 OKLAHOMA	71 GREECE
36 OREGON	72 FRANCE
	73 USA (NOS)

frequency distributions for all variables and descriptive statistics including mean, median, standard deviation, and standard error of the mean for continuous variates. The findings for all study factors other than OTs and OTGs are presented in the first analysis chapter, followed by the presentation of findings from the detailed work histories in the second.

The basic procedure used for analysis was an examination of effect measures for various factors and/or the presentation of the differences in the distribution of variables between cases and controls. The former was accomplished mainly through extensive use of the Mantel-Haenszel Odds Ratio (OR) for matched studies with a variable number of controls per case and is the case-control equivalent of the relative risk estimate derived from cohort studies. As such, it can be considered a measure of effect although we have not, strictly speaking, directly measured this effect. The presentation of the odds ratio and its associated confidence interval is descriptive and, for this investigation, the effect measure was not considered statistically significantly elevated if the 90% interval included one, which is the null value for an odds ratio or relative risk. The confidence interval itself was 'test-based' because it was calculated using the formula which is derived from the data or 'test' of hypothesis being conducted.

The major procedure for the second type of analysis, where distributions and summary statistics of variates are considered, was the Paired T-Test. This procedure was the one of choice, and was used whenever possible, because it makes full use of continuous data and because it is a statistically valid procedure for the analysis of data generated from a matched design. The former reason is quite important in light of the fact that utilization of the program available at the OHSU for the calculation

of ORs and their associated tests of significance forces the investigator not only to categorize but to dichotomize the exposure or the putatively causal factor, a procedure which leads to loss of information and which is anathema to epidemiologic investigations. While the Paired T-Test does not utilize a direct equivalent of an OR, it does not, at the same time, lead to inefficiency and does allow for a statistical test of the significance of the mean differences of the variable between the groups being compared, this latter being an indirect measure of effect."

It should be added here that the T-Test was conducted in a manner which differed somewhat from the usual procedure because the difference between a case and its controls was based on an average value for the controls. Since all cases did not necessarily have a full complement of controls, the average is not based on a constant number of controls which means that the assumption of normality is not being met precisely, but this slight departure from normality was not considered very damaging because of the robustness of the Paired T-Test procedure.

The major measures of effect, then, are odds ratios and comparisons of distributions and summary statistics such as means. When using these procedures, control for confounders was accomplished by stratifying on these factors in the analysis and examining the odds ratios or p-values for the T-Tests at different levels of the confounder, bearing in mind that control for some potential confounders (age, race, sex, duration) was accomplished in the design by matching on these factors. For instance, an OR for a specific exposure was calculated separately for native and foreign-born subjects and, if these ORs were pragmatically similar, an overall non-nativity-specific OR was then presented. It was felt that a test for homogeneity of odds ratios across strata would not be very helpful since we were more interested in practical, rather than statistical,

significance when considering the pooling of strata for the presentation of findings. When stratum-specific rates differ considerably, the reader's attention is directed toward this difference and the measures of effect are presented separately.

We were naturally concerned with interactions between factors and their possible effects and, while statistical tests for interactions were generally not used, decisions were based on an assessment of their practical effects after examining different combinations of the interacting variables. For instance, after determining that an OR differed neither between sexes nor between nativity groups, the ORs were examined for combination of these variables (e.g., female native-born, female foreign-born, male native-born, etc.) and decisions concerning data pooling were based on these examinations.

Two final comments regarding statistical tests are in order here. First, two-tailed probability tests were most often used because of the hypothesis-generating nature of this investigation, resulting in our inability to consistently predict the nature and direction of the differences. Second, 90 and not 95 per cent confidence intervals were calculated for the odds ratios so occasionally an interval whose lower bound is greater than unity is not starred as significantly elevated since the chi statistic is used for the purpose of establishing statistical significance.

ANALYSIS I: DEMOGRAPHIC AND OTHER FACTORS

This chapter will present the general descriptive findings along with the analytic results which do not deal directly with the detailed work histories on which both exposures and OTs (Occupational Titles) are based. These latter will be exhaustively examined in the following chapter.

Matched Variables

Subjects were matched on factory (A or B), age (year of birth and age at death, both within three), race, sex, and, for one control group (ARSD), duration of employment. An edit program run on the study file indicated that the matching constraints had been executed properly during the subject selection procedures, resulting in similar distributions for these factors among both cases and controls. It is of interest, nonetheless, to present these distributions in describing the general attributes of the subjects included in this study.

In total, the study included 495 subjects- 52 cases and 197 controls in Company A and 50 cases and 196 controls in Company B. While the original design called for four controls for each case, suitable comparands could not be found in 15 instances, as is obvious from the totals presented above. Despite this inability, cases were not excluded unless it was impossible to find at least one control for each of the two control groups.

Overall, 46 subjects, or approximately 10 per cent, were females, including 10 cases and 36 controls. From this can be seen that it was

relatively more difficult to find controls for females since they comprise 10 per cent of the study population but they account for 25 per cent of the unsuccessful attempts at matching which is probably due to the rather small pool of women employed in the industry.

A slightly smaller proportion of subjects (41 or 8 per cent) were black, and this group was comprised of 9 cases and 32 controls. All blacks in this study were males and a disproportionate number of these subjects (32) had been employed by Company A. More than half (8 of 15) of the missing controls, therefore, were not found for cases who were either female (all of whom were white) or black males. Table 23 summarizes the race and sex distribution of all subjects.

Marital Status

Overall, 77 percent of cases and 83 per cent of all controls were married at the time they were first employed, and the company-specific rates are quite similar to these, as an examination of Tables 24-26 indicates. It should also be noted that, in both companies, the proportion of cases who were separated or divorced, and the proportion widowed, was approximately twice that of controls, although the numbers in these categories are quite small.

At the time of death, from available death certificates, 68 per cent of Company A cases and 75% of those in Company B were still married, while 27 and 22 per cent, respectively, were either widowed or divorced.

Education

There were no striking overall or company-specific differences in educational attainments of cases and controls, as an examination of

Tables 27-29 will reveal with about 75 per cent of both groups having completed only junior high school or less. In general, Company B subjects completed more years of schooling than those in Company A, especially as regards the proportion who completed their high school education. This may be partly due to the fact that 7 of the 9 black cases and 25 of the 32 controls in this race group were employed at Company A and only one member of this group had graduated junior high school, with the great majority of the remaining ones having a grade school education or less.

Cases in both companies tended to have slightly fewer years of schooling than controls, with most subjects having formal education less than high school. It should be remembered, however, that many of the subjects in this study were of school age early in the century when high school completion was not common, a fact which, along with the blue-collar status of employees, doubtless explains the reported levels of formal education received. It should also be mentioned that a fair proportion of subjects had been born in foreign countries, most of whom were born in Europe where one year of education may be more than the equivalent of one year of American education. It should finally be noted that females, as expected, had received less education than males, but since the number of females was approximately equal in both companies, this had no effect on the differences in company-specific educational attainments.

We also conducted a further analysis of Socio-Economic Status (SES) by using Job Codes within Company A, with which were associated evaluations on 12 factors, including education, skill, initiative, and experience. These codes were introduced in 1949, so a relatively small proportion of jobs within our study were eligible for inclusion in this analysis. After

extensive efforts in creating the file for this analysis, however, we observed a score for only one of the 52 cases within this company, while over half the controls had scores. Because of the dearth of scores among cases, the analysis was impossible.

Life Status and Age at Death

Stomach cancer case identification for this study was based on mortality data, so all cases are deceased. The age match, however, was based on two factors: year of birth, ± 3 and age at death, for which the control must have been at least as old as the case (± 3) if the control was deceased. According to this constraint, however, the controls could have still been alive at the time they were selected and many, in fact, were. Table 30 presents the distributions of age at death for the cases and decedent controls and of age as of 1 January 1976 for living controls, as well as the number and proportion of controls in the latter category.

As is seen, 75 per cent of the controls were still alive on the closing date of the study, and many in this group have already attained very advanced ages. In addition, a greater proportion of the deceased controls attained older ages than did the cases. These findings, as indicated, are doubtless explained by the matching constraints.

The ages of subjects at death were further analyzed according to pathology, and the mean among confirmed cases (70.5) was virtually equal to the mean age at death among the unconfirmed cases (71.5). In addition, the cumulative proportions of cases dying by the age of 65 were nearly equal in the pathology groups (22 vs. 21 per cent) as were the cumulative proportions dying by the age of 80 (91 vs. 84 per cent). Overall, the mean age at death of Company A cases was 70.4, while among those at Company B, the average age at death was 71.4.

Place of Birth

Ascertainment of the birthplace of subjects in this study was exceptionally good, with only one unknown among the 495 subjects. Overall, 22 per cent of all cases and 17 per cent of controls were foreign born, although there were differences in these proportions between the two companies. In Company A, 25 per cent of the cases and 23 per cent of all controls were foreign born, while the respective proportions in Company B were 20 and 12 per cent, a finding which may indicate different hiring policies at Company A. For both companies, then, the proportion of foreign born among cases was greater than among controls, with this trend holding for three of the four control groups, the only exception being the ARSD control group at Company A where 32 per cent of the controls in this group were not born within the United States. It should also be noted here that three of the ten female cases and seven of the thirty six female controls were foreign born and these proportions are quite similar to those among males. In addition, as expected, all black subjects were native born.

Nativity is a factor of much importance in this study since it may, by itself, account for the excess of mortality from gastric cancer among employees of the rubber industry; further analysis of this variable is therefore appropriate. The list of foreign countries in which subjects were born (Table 31), which numbered 21, was divided into tertiles according to mortality from stomach cancer, using Doll's (3) male age-adjusted international mortality rates for this disease. High risk countries had death rates of 75 per hundred thousand and above, intermediate risk countries had rates between 50-74, and those classified as low risk countries had death rates below 50. Before examining the

results, however, numerous limitations should be stated. First, the mortality rates used for creation of the risk categories are based on age-standardized rates for males between the ages of 45 and 64 years. In our study, however, only 22 of the 102 cases (22 per cent) died at an age below 65, leaving open the possibility that the ranking procedure might have differed from the one used if the age-standardized mortality experience for all, and not just the younger, age groups had been used as the basis of the categorization. Second, assumptions concerning two of the countries on the list were made: people born in 'Germany' were assumed to have been born in what is presently West Germany, while those subjects born in 'Austro-Hungary' were assumed to have mortality rates somewhere between those of what is presently Austria and Hungary.

An examination of the distributions presented in Table 32 reveals very little difference in nativity risk between cases and controls, with 48 per cent of cases and 46 per cent of controls having been born in countries categorized as being at high risk of mortality from stomach cancer. Similarly, the proportions born in countries with moderate and low risks are also essentially equal. Hasty conclusions should not be drawn from these data, however since the factor of most importance is that a greater proportion of cases were born in foreign countries, and all of these countries have higher mortality rates than those of the United States.

Because of the limitation concerning the age range of mortality rates on which the risk stratification was based, use was made of World Health Organization (129) age-specific data for the available 13 of the 21 countries in which subjects were born. Table 33 presents mortality rates for age groups 65-74 and 75 and above. The data for each of these age groups was used, independently, to generate risk

rankings and a comparison of these separate distributions is presented. When using the younger age range as the basis for the rankings, the categories are almost exactly the same as those based on Doll's rates, while there are appreciable differences in the ranking of countries based on the older age group. In addition, the proportion of cases and controls in each of the risk categories in the categorization based on mortality among the younger males are essentially equal and very similar to those which use Doll's data, although there is some divergence of proportions in the ranking based on mortality among those aged 75 and over.

When these data were analyzed separately for confirmed (64 cases) and unconfirmed (38 cases), the results indicated that 17 (27 per cent) of the confirmed cases and 6 (16 per cent) of the unconfirmed cases had been born in foreign countries. Using the risk categorization based on Doll's data, we get the results presented in Table 34, from which we can see that among confirmed cases and their matched controls a greater proportion of cases (9 or 53 per cent) were born in high risk countries than their matched controls (17 or 40 per cent), in addition to which a greater proportion of confirmed cases (53 per cent) compared with those who were unconfirmed (33 per cent) were born in countries at high risk of mortality from stomach cancer. When confirmed cases and their matched controls are further analyzed, however, we see that the cumulative proportion through the moderate category are essentially equal (88 vs. 85 per cent) while among the unconfirmed cases and their matched controls, the cumulative proportion in these two categories is higher for the controls (66 vs. 85 per cent).

The birthplaces of native American subjects were further examined to see if cases were more likely to have been born in states with

higher death rates. As expected, the greatest proportion of subjects was born in Ohio. This proportion is 22 per cent and is the same for both cases and controls separately. The two states in which the next greatest proportion of subjects was born are West Virginia and Pennsylvania, in which a combined proportion of 31 per cent of the cases and 26 per cent of the controls were born. In fact, approximately half of all subjects had been born in one of these three states.

All states in the continental United States were then categorized into one of three groups according to death rates among white males (5), and the results of this stratification are presented in Table 35. As can be seen, a slightly higher proportion of both confirmed and unconfirmed cases had been born in high risk states, although the differences between these proportions, and the differences in death rates between the states, are not striking and there does not appear to be much difference in the distributions according to pathology status, as well.

It should be mentioned here that one might object to all the categorizations of risk presented here because the mortality rates on which they are based are all rather recent, while the subjects had left these areas, for the most part, long ago. This objection, however, is not disturbing because the relative rankings, and not the absolute values, are the major concern and these rankings seem to be rather consistent temporally.

One final analysis was performed because of Mancuso's (130) finding that there is an excess of deaths from stomach cancer among the southern-born who have migrated to Ohio. Among subjects from Company A, 17 of the 52 cases (33 per cent) and 85 controls (43 per cent) had been

born in the South (South Atlantic, East South Central, West South Central) while the comparable figures for Company B were 34 and 38 per cent, respectively.

In summary, then, the only important differences in nativity between cases and controls is in the overall proportion born in foreign countries, although even this difference is not great. Among these subjects, however, approximately equal proportions were born in countries with high, intermediate, and low mortality rates from stomach cancer, while among native born subjects the same conclusions can be drawn regarding states.

Underlying Causes of Death

The inclusion criteria for cases in this study was the listing of stomach cancer anywhere on the death certificate. As expected, however, it was listed most frequently (89 of 102 or 87 per cent) as the underlying cause of death, as reference to Tables 36-37 indicates, with the second most frequently mentioned underlying cause of death being ischemic heart disease (ICDA 410-414), which appeared on five per cent of the death certificates.

Controls were eligible for inclusion only if there was no mention of a malignancy anywhere on their death certificates, if deceased. Examination of Table 37 reveals that of the 96 decedent controls, 56 (58 per cent) had ischemic heart disease mentioned as the underlying cause of death, followed by cerebrovascular diseases (ICDA 430-438), diseases of the arteries (ICDA 440-448), and emphysema (ICDA 492) so that 76 of the decedent controls (79 per cent) died of circulatory diseases. The disproportionate number dying from ischemic heart disease is not surprising in light of the control selection restriction regarding malignancies.

Pathology Data

As described earlier, the four major hospitals in the Akron area to which cases of stomach cancer were likely to have gone for treatment were searched for records of the cases included in this study, and we were able to gather some confirmatory evidence for the disease, as stated on the death certificate, for 64 of the 102 (63 per cent) cases included in this study, with confirmation based on evidence from either autopsy, histology, radiology, surgery, or clinical impressions. In addition to this information, data on type of cancer and site of the disease within the stomach were collected, and these findings are summarized in Table 38. In examining the section describing the methods of diagnosis, it should be kept in mind that the order of precedence for the listing presented is: autopsy, histology, surgery, radiology, and clinical impressions.

An examination of this table indicates that 56 of the 64 (88 per cent) confirmed cases were verified on the basis of either pathology or autopsy reports, the two methods generally thought to be the most reliable method of diagnosis. In addition, 55 of the 69 cases (86 per cent) for whom the specific diagnosis was known were classified as having adenocarcinoma of some form, including well or moderately differentiated and poorly or undifferentiated adenocarcinoma, a finding which agrees closely with other published reports, including Ming's (75) findings cited earlier. The finding that 18 of the 35 cases (51 per cent) for whom the specific site within the stomach was established had the lower third or pyloric region indicated was also in general agreement with Stout's (76) reported findings. When these factors were examined separately by company, there was no overall difference in the proportion

of verified cases, but among subjects for whom pathology data were available a greater proportion of Company A Subjects (12 of 34 or 35 per cent) had the cancer in the pyloric region of the stomach than did those at Company B (6 of 31 or 19 per cent).

Calendar Year of Hire

Calendar year of hire is an important factor because of the possibility that gastric carcinogens may have been either introduced or eliminated in different calendar years. Any significant differences between cases and controls, therefore, in year of hire would be of interest and would require further examination.

Overall, approximately half of cases and controls had entered the industry by 1929. This was followed by a relatively small proportion entering during the next decade and a large number entering during the period 1940-1949, almost all of whom had begun working in the industry during the war years, probably immediately after discharge from the service.

While the general pattern of entry is similar in both companies, there are differences worth noting. At Company A the largest proportion of both cases and controls (40 per cent) entered during the 1920 decade, followed by the 1940 and 1910 decades. At Company B, on the other hand, entry was much more common during the years 1910-1919 (approximately 40 per cent) and this was followed by entry into the industry during the 1920 and 1940 decades. It should be noted here, however, that while there were major inter-company differences, the proportions of cases and controls beginning their employment within the industry within each

company separately were quite similar, as an examination of Tables 39-41 will reveal except for entry into Company A during the first decade. It should also be noted that none of the female cases, and no black subjects (both cases and controls) had entered the industry during the first decade (1910-1919) of plant operations at both companies.

To further analyze for differences in this important factor, Paired t-tests were performed on the groups to be described, with the slight modification of using an average for the controls in any given stratum (a case and its matched controls), and a two-tailed test of significance was used since we could not always predict the direction of the expected difference. Results of this analysis are presented in Table 42 from which it can be seen that only in the comparison of cases with ARSD controls at Company A were the differences in year of hire statistically significant and this difference is probably reflected in the different entry rates for the first decade of plant existence. Further analysis of the sex-and race-specific differences and their probabilities revealed that statistical significance for this difference was maintained among confirmed white male cases at Company A only ($p = 0.022$) and not for white females and black males, although the numbers in the latter two categories are small. While the difference in entry year between white male cases and controls did achieve statistical significance, however, the practical importance of this difference (3.0 years) is questionable, although it should be added that this finding was initially interesting because it occurred in the comparison of cases with ARSD-matched controls, the 'D' of course signifying that these controls were matched on total duration of employment as well as on the other three factors. This interest diminishes, however, because of the

statistically non-significant differences for the comparisons with the ARS group and with both groups in Company B and because, while the group was matched on duration, the estimate of duration was indirect and was based on a surrogate measure, as described in Materials and Methods.

Further analysis according to pathology confirmation status did not alter any of the findings described and the distributions are presented in Tables 43-44 . Generally, there were non-significant differences between cases and controls within both the confirmed and unconfirmed groups, with cases tending to have started slightly earlier than controls. A comparison across these groups revealed that unconfirmed cases had started their employment within the industry at a slightly earlier calendar period than those cases whose illness was confirmed.

After these analyses had been completed, we decided to look a bit more closely at the group in Company A, comprised of 11 cases and 21 controls, which had entered the industry during the first decade (1910-1915) of existence of the plant in Akron, because there had been a disproportionate number of cases in this group, as reference to Table 39 will confirm. Because the only significant differences within Company A occurred in the comparison of subjects in this company with ARSD controls, the following description will be limited specifically to this group.

All subjects in this group were white males. Five of the 11 cases (45%) and 8 of the 20 ARSD controls (40%) were foreign-born while only 8 of the remaining 41 cases (20%) and 23 of the 76 controls (30 %) who entered the plant after the first decade had been born in countries other than the U.S. It is therefore apparent that all subjects, including both cases and controls, who entered the plant during the first decade were more likely to have been foreign-born than those who entered after the first decade.

The analysis of other important factors reveals striking differences both between cases and their matched controls who entered during the years 1910-1919 and between subjects who entered during this period compared with those entering later, with a summary of these findings appearing in Table 45. As can be seen, first decade of entry cases worked approximately 70 months longer than their ARSD matched controls (385 vs. 317) in active OTs and began at an age approximately 9 years younger (25 vs. 34). In addition to these findings, we also see that these cases worked longer and started younger than the remaining cases as well. While the age at death of these cases was about 8 years older than the remaining cases, we must remember that the design called for inclusion of cases who had died only during the decade 1964-1973. Since these cases started earliest, they would be expected to have lived longest. Age at death of controls is not presented because most were still alive and because the constraint was that they must have lived at least as long (or longer) than the case, making a comparison meaningless.

Further examination of this group revealed one additional interesting finding: The overall significant differences between cases and ARSD controls in age at hire, and year of hire are accounted for entirely by this group which entered during the first decade. When this is further examined by pathology confirmation status, these significant differences persist only among the 6 confirmed cases, which means that the overall significant differences described earlier are explained entirely by this one small group of cases and their matched controls. These results are summarized in Table 46 .

Total Duration of Employment

As just reiterated, the matching procedure for total duration of employment was based on the difference between the last year employed and the seniority year which is a reasonable, but not an exact, measure of duration. For this analysis, however, total duration was based on time spent within active OTs, which excludes sick leaves, leaves of absence, military duty, etc. Tables 47-51 present the distributions for these variables, in months, from which it can be seen that the overall means (358 vs. 353) and the medians (386 vs. 369) are remarkably similar, as are the general distributions of the categorized values for this factor. Once again, however, there are some differences between companies, with subjects from Company B having somewhat longer durations than those from A, although the intra-company differences between cases and controls, like the overall differences, are rather small and inconsequential.

The results of the t-tests are presented in Table 52 , and an examination of these findings again indicates that the differences in total duration of employment in active OTs is neither statistically nor practically significant. In fact, the greatest discrepancies, albeit small, were found in the comparison of cases with ARSD controls, again noting that this group was matched on duration of employment. Once again, the explanation probably lies in the fact that the matching procedure was based on an indirect determination of the value for this variable.

When these data were further examined according to pathology status, we found that confirmed cases had worked slightly longer than unconfirmed cases, but this difference did not appear to be of practical significance,

while the differences within groups were neither of practical nor statistical significance.

Despite the fact that one control group (ARSD) was matched on duration of employment while the other (ARS) was not, the duration within active OTs did not differ much between cases and both control groups separately and combined, nor did it differ much between control groups themselves. To test this, paired t-tests were performed on the difference between the mean total durations in active OTs of the ARS vs. ARSD control groups. These differences were minimal and not statistically significantly different. Accordingly, in subsequent analyses the distinction between the two control groups will be ignored.

Age at Hire

Age at hire is a factor of particular importance because of the generally held belief that the younger the age at which exposure to a carcinogen begins the greater the risk of developing cancer. Tables 53-57 display the proportions of subjects in different categories of this variable, and we once again observe remarkable similarities in the means and medians of this variable in both overall and company specific findings, with slight differences between companies. In general, subjects began working in the industry around the age of 30, with Company B subjects beginning work at a slightly younger age than those at Company A, the difference being approximately three years. A closer examination of the distributions, however, reveals that the cumulative frequencies for 'Age at Hire' before the age of 29 are greater for cases in both companies, and the proportions of cases hired at the youngest ages are

also greater than the corresponding proportions for controls.

These apparent differences mostly disappear, however, when results of the Paired t-test presented in Table 58 , a procedure which maintains the integrity of the matched strata, are examined. These results again indicate no statistically significant differences between cases and controls, except for the comparison of cases with ARSD controls at Company A, where the difference approaches statistical significance ($p = 0.02$) but probably not practical significance. Further analysis, as with the previously discussed factor, again indicates that a statistically significant difference in this group was found only among white males ($p = 0.027$) and not among black males or white females. It is worth noting, however, that while the differences between cases and controls were indeed slight, cases had been consistently hired at younger ages than controls.

As with the variables described previously, separate analyses for confirmed and unconfirmed cases and their matched controls did not reveal any appreciable differences, and whatever discrepancies did exist were not statistically significant.

TABLE 23

RACE AND SEX DISTRIBUTION OF SUBJECTS

All Cases

	<u>White</u>	<u>Black</u>	<u>Total</u>
Males	83	9	92
Females	<u>10</u>	-	<u>10</u>
Total	93	9	102

All Controls

	<u>White</u>	<u>Black</u>	<u>Total</u>
Males	325	32	357
Females	72	-	36
Total	361	32	393

TABLE 24

MARITAL STATUS OF SUBJECTS AT EMPLOYMENT

1. COMPANY A CASES VS. CONTROLS

<u>Marital Status</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
Single	8	15.4	20	10.2
Married	37	71.2	167	84.8
Sep/Div	3	5.8	6	3.0
Widowed	<u>4</u>	<u>7.7</u>	<u>4</u>	<u>2.0</u>
Totals	52	100.0	197	100.0

TABLE 25

MARITAL STATUS OF SUBJECTS AT EMPLOYMENT

2. COMPANY B CASES VS. CONTROLS

<u>Marital Status</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
Single	0	0.0	14	7.1
Married	41	82.0	158	80.6
Sep/Div	3	6.0	9	4.6
Widowed	4	8.0	8	4.1
Unknown	<u>2</u>	<u>4.0</u>	<u>7</u>	<u>3.6</u>
Totals	50	100.0	196	100.0

TABLE 26

MARITAL STATUS OF SUBJECTS AT EMPLOYMENT

3. ALL CASES VS. ALL CONTROLS

<u>Marital Status</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
Single	37	36.3	181	46.1
Married	49	48.0	178	45.3
Sep/Div	6	5.9	15	3.8
Widowed	8	7.8	12	3.0
Unknown	<u>2</u>	<u>2.0</u>	<u>7</u>	<u>1.8</u>
Totals	102	100.0	393	100.0

TABLE 27

EDUCATIONAL ATTAINMENTS OF SUBJECTS

1. COMPANY A CASES VS. CONTROLS

<u>Education</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
Grad. Crade Schl.	26	50.0	117	59.4
Some Jr. High	10	19.2	36	18.3
Grad. Jr. High	7	13.5	18	9.1
Some High Schl.	1	1.9	5	2.5
Grad. High Schl.	0	-	1	0.5
Unknown	<u>8</u>	<u>15.4</u>	<u>20</u>	<u>10.2</u>
Totals	52	100.0	197	100.0

TABLE 28

EDUCATIONAL ATTAINMENTS OF SUBJECTS

2. COMPANY B CASES VS. CONTROLS

<u>Education</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
Grad. Grade Schl.	6	12.0	26	13.3
Some Jr. High	24	48.0	83	42.3
Grad. Jr. High	3	6.0	17	8.7
Some High Schl.	5	10.0	26	13.3
Grad. High Schl.	3	6.0	22	11.2
Some Coll/Tech	1	2.0	1	0.5
No Education	2	4.0	1	0.5
Unknown	<u>5</u>	<u>10.0</u>	<u>20</u>	<u>10.2</u>
Totals	50	100.0	196	100.0

TABLE 29
EDUCATIONAL ATTAINMENTS OF SUBJECTS
3. ALL CASES VS. ALL CONTROLS

<u>Education</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
Grad. Grade Schl.	32	31.4	143	36.4
Some Jr. High	34	33.3	119	30.3
Grad. Jr. High	10	9.8	35	8.9
Some High Schl.	6	5.9	31	7.9
Grad. High Schl	3	2.9	23	5.9
Some Coll/Tech	1	1.0	1	0.3
No Education	3	3.0	1	0.3
Unknown	<u>13</u>	<u>12.7</u>	<u>40</u>	<u>10.2</u>
Totals	102	100.0	393	100.0

TABLE 30

LIFE STATUS AND AGE AT DEATH OF SUBJECTS

LIFE STATUS OF CONTROLS AS OF 1 JAN 76

	<u>Number</u>	<u>Proportion</u>
Alive	295	75
Dead	98	25
Total	393	100

<u>Age</u>	<u>Cases</u>		<u>Controls</u>		<u>Controls</u>	
	<u>Age at Death</u>		<u>Age at Death</u>		<u>Age on 1 Jan 76</u>	
	<u>#</u>	<u>Per Cent</u>	<u>#</u>	<u>Per Cent</u>	<u>#</u>	<u>Per Cent</u>
40-49	1	1.0	-	-	-	-
50-59	13	12.7	4	4.1	12	4.1
60-64	8	7.8	2	2.0	15	5.1
65-69	18	17.6	6	6.1	35	11.9
70-74	24	23.5	17	17.3	54	18.3
75-79	23	22.5	31	31.6	56	19.0
80-84	13	12.7	29	29.6	82	27.8
85+	<u>2</u>	<u>2.0</u>	<u>9</u>	<u>9.2</u>	<u>41</u>	<u>13.9</u>
Totals	102	100	98	100	295	100

TABLE 31

BIRTHPLACE

1. ALL CASES VS. ALL CONTROLS

Birthplace	Cases		Controls	
	Frequency	Per Cent	Frequency	Per Cent
U.S.	78	76.5	325	82.7
Foreign	23	22.5	68	17.3
Armenia	-		2	
Austria	3		6	
Austro-Hung	1		5	
Czechoslovakia	1		5	
England-Wales	3		5	
France	1			
Germany	1		3	
Greece	1			
Hungary	2		9	
Ireland	1			
Italy	3		17	
Lithuania	-		1	
Poland	2		2	
Rumania	-		3	
Russia	2		1	
Scotland	1			
Sweden	-		1	
Syria	-		1	
Turkey	-		3	
W. Ukraine	-		1	
Yugoslavia	1		3	

TABLE 32

NUMBER AND PROPORTION OF FOREIGN-BORN SUBJECTS BORN IN
DIFFERENT RISK CATEGORIES FOR MORTALITY FROM STOMACH CANCER¹

HIGH Risk Countries (SDR* ≥ 75)

Country	SDR	Cases		Controls	
		Number	Per Cent	Number	Per Cent
Russia	128	2	8.7	1	1.5
Poland	96	2	8.7	2	2.9
Czechoslovakia	87	1	4.3	5	7.4
Hungary	86	2	8.7	9	13.2
Romania	84	-	-	2	2.9
Ukraine	77	-	-	1	1.5
Austria	75	3	13.0	6	8.8
Austro-Hungary	(75-86)	1	4.3	5	7.4
Totals		11	48.0	31	46.0

MODERATE Risk Countries (SDR = 50-74)

Italy	68	3	13.0	17	25.0
Germany	65	1	4.3	3	4.4
Lithuania	62	-	13.0	1	1.5
Scotland	54	1	4.3	-	-
England-Wales	50	3	13.0	5	7.4
Totals		8	35.0	26	38.2

LOW Risk Countries (SDR < 50)

Yugoslavia	49	1	4.3	3	4.4
Ireland	49	1	4.3	3	4.4
France	42	1	4.3	-	-
Armenia	46	-	-	2	2.9
Sweden	38	-	-	1	1.5
Greece	31	1	4.3	-	-
Totals		4	17.4	9	13.2

UNKNOWN Risk

Syria	-	-	-	1	1.5
Turkey	-	-	-	1	1.5
	-	-	-	2	2.9

1. SDRs from Doll R: Worldwide distribution of gastrointestinal cancer.
Nat Can Inst Mono 25, 1968

* SDR = Standardized Death Rate per 100,000

TABLE 33

AGE- AND COUNTRY-SPECIFIC DEATH RATES (PER 100,000)
FROM STOMACH CANCER AMONG MALES
AND RISK CATEGORIZATIONS BASED ON THESE RATES

Country	Mortality per 100,000	
	65-74	75+
Austria	251	439
Czechoslovakia	263	432
England-Wales	154	247
France	117	242
Germany	204	429
Greece	100	160
Hungary	274	464
Italy	217	379
Poland	274	342
Rumania	221	261
Sweden	121	286
Scotland	149	227
Yugoslavia	165	215

CATEGORIZATION BASED ON RATES FOR YOUNGER MALES¹

High Risk			Moderate Risk			Low Risk		
Country	Cases	% Controls	Country	Cases	% Controls	Country	Cases	% Controls
Hungary	10.5	16.7	Italy	15.8	31.5	Scotland	5.3	-
Poland	10.5	3.7	Germany	5.3	5.6	Sweden	-	1.8
Czechoslovakia	5.3	9.3	Yugoslavia	5.3	5.6	France	5.3	-
Austria	15.8	11.1	Eng-Wales	15.8	9.3	Greece	5.3	-
Rumania	-	5.6						
Totals	42	46		42	52		16	2

CATEGORIZATION BASED ON RATES FOR OLDER MALES

Hungary	10.5	16.7	Poland	10.5	3.7	France	5.3	-
Austria	15.8	11.1	Sweden	-	1.8	Scotland	5.3	-
Czechoslovakia	5.3	9.3	Rumania	-	5.6	Yugoslavia	5.3	5.6
Germany	5.3	5.6	Eng-Wales	15.8	9.3	Greece	5.3	-
Italy	15.8	31.5						
Totals	53	74		26	20		21	6

1. Mortality Rates from World Health Statistics Annual 1: Vital Statistics and Causes of Death, World Health Organization, Geneva, 1976

TABLE 34

BIRTHPLACE OF SUBJECTS ACCORDING TO RISK CATEGORIZATION
AND CONFIRMATION STATUS

Confirmed Cases (N = 64)

	<u>Number</u>	<u>Per Cent</u>	<u>Matched Controls</u>	
High Risk	9	53	17	40
Moderate Risk	6	35	19	45
Low Risk	<u>2</u>	<u>12</u>	<u>6</u>	<u>15</u>
Totals	17	100	42	100

Unconfirmed Cases (N = 38)

	<u>Number</u>	<u>Per Cent</u>	<u>Matched Controls</u>	
High Risk	2	33	15	58
Moderate Risk	2	33	7	27
Low Risk	<u>2</u>	<u>33</u>	<u>4</u>	<u>15</u>
Totals	6	100	26	100

TABLE 35

BIRTHPLACE OF NATIVE AMERICAN SUBJECTS, BY PATHOLOGY

CATEGORIZATION OF STATES¹

1. High Risk - Death Rate > 16 per 100,000
Conn, Ill, Maine, Mass, Mich, Minn, NH, NJ, NM, NY, ND, Penn, RI, SD, Wis
2. Moderate Risk - Death Rate 13 and 16
Cal, Col, Idaho, Iowa, La, Md, Mont, Neb, Nev, Ohio, Or, Utah, Ver, Wash,
W Va, Wy
3. Low Risk - Death Rate < 13
All other states and D.C., except Alaska and Hawaii

Confirmed Cases and Matched Controls

	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
High Risk States	12	25	36	17
Moderate Risk	21	45	102	49
Low Risk	14	30	69	33
Totals	47	100	207	100

Unconfirmed Cases and Matched Controls

	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
High Risk	7	23	23	20
Moderate Risk	17	54	49	42
Low Risk	7	23	45	38
Totals	31	100	117	100

1. Based on white male death rates in Cancer by County [5]

TABLE 36
 UNDERLYING CAUSES OF DEATH
 1. ALL CASES

<u>UCD</u>	<u>ICDA Code</u>	<u>Frequency</u>	<u>Per Cent</u>
Malig. Neo. Esoph.	150	1	1.01
Malig. Neo. Stom.	151	89	87.2
Malig. Neo. Sm. Int.	152	1	1.0
Malig. Neo. Skin	173	1	1.0
Lymph. & Hema. Neo.	202	1	1.0
Isch. Heart Disease	410-414	5	5.0
Sympt. Heart Dis.	427	1	1.0
Dis. of Art.	447	1	1.0
Sen and Ill-Def. Dis.	796	1	1.0
Unknown	-	<u>1</u>	<u>1.0</u>
Totals		102	100.0

TABLE 37
UNDERLYING CAUSES OF DEATH
2. ALL CONTROLS

<u>UCD</u>	<u>ICDA Codes</u>	<u>Frequency</u>	<u>Per Cent</u>
Lymph. & Hemat. Neo.	202	1	1.0
Diabetes Mellitus	250	3	3.1
Hypertensive Disease	404	1	1.0
Ischemic Hrt. Dis.	410-414	56	58.3
Sympt. Hrt. Dis.	427	1	1.0
Ill-def. Hrt. Dis.	429	1	1.0
Cerebrovasc. Dis.	430-438	11	11.5
Dis. of Art.	440-448	5	5.2
Phleb. and Thrombo.	451	1	1.0
Pneumonia	480-486	2	2.1
Emphysema	492	5	5.2
Othr. Dis. of Resp. Sys.	510-519	2	2.1
Acute Append.	540	1	1.0
Intest. Obs.	560	1	1.0
Othr. Liver Dis.	573	1	1.0
Chron. Nephritis	582	1	1.0
Ill-Def	796	1	1.0
Fract of Humerus	812	1	1.0
Open Back Wound	876	<u>1</u>	<u>1.0</u>
Total	-	96	100.0
Alive ¹	-	290	

¹These subjects were still alive on 01/01/76, the termination date of the study.

TABLE 38
SUMMARY OF PATHOLOGY FINDINGS

<u>Method of Diagnosis</u>	<u>Number</u>	<u>Per Cent</u>
Autopsy	6	6
Histology	50	49
Radiology	4	4
Surgery	4	4
Clinical	2	2
Death Certificate Only	<u>38</u>	<u>37</u>
Totals	102	100

<u>Type of Cancer</u>	<u>Number</u>	<u>Per Cent</u>
Adenocarcinoma, NOS	40	39
Un- or poorly differentiated Adenoca	10	10
Well differentiated Adenoca	5	5
Carcinoma or Cancer, NOS	9	9
Other	5	5
Unknown	<u>33</u>	<u>32</u>
Totals	102	100

<u>Site Within Stomach</u>	<u>Number</u>	<u>Per Cent</u>
Upper Third (cardia and fundus)	10	10
Mid Third (body)	7	7
Lower Third (pylorus)	18	18
Other Combination	5	5
Unknown	<u>62</u>	<u>61</u>
Totals	102	102

TABLE 39

FIRST CALENDAR YEAR IN THE INDUSTRY

1. COMPANY A CASES VS. CONTROLS

<u>Calendar Year</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
1910-1919	11	21.1	23	11.7
1920-1929	21	40.4	78	39.6
1930-1939	2	3.8	22	11.1
1940-1949	17	32.7	70	35.5
1950-1959	<u>1</u>	<u>1.9</u>	<u>4</u>	<u>2.0</u>
Totals	52	100.0	197	100.0

TABLE 40

FIRST CALENDAR YEAR IN THE INDUSTRY

2. COMPANY B CASES VS. CONTROLS

<u>Calendar Year</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
1910-1919	21	42	73	37.3
1920-1929	16	32	71	36.2
1930-1939	1	2.0	5	2.6
1940-1949	11	22.0	40	20.4
1950-1959	<u>1</u>	<u>2.0</u>	<u>7</u>	<u>3.6</u>
Totals	50	100.0	196	100.0

TABLE 41

FIRST CALENDAR YEAR IN THE INDUSTRY

3. ALL CASES VS. ALL CONTROLS

<u>Calendar Year</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
1910-1919	32	31.4	96	24.4
1920-1929	37	36.3	149	37.9
1930-1939	3	3.0	27	6.9
1940-1949	28	27.5	110	28.0
1950-1959	<u>2</u>	<u>2.0</u>	<u>11</u>	<u>2.8</u>
Totals	102	100.0	121	100.0

TABLE 42

PAIRED T-TESTS FOR YEAR OF HIKE

<u>OVERALL</u>							
COMPARISON	<u>Mean</u>		<u>S.D.</u>		<u>S.E.</u>		Two-Tailed Probability
	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	
All Cases vs. All Controls	1928.0	1929.0	11.0	8.7	1.1	0.9	0.242
All Cases vs. All ARS Controls	1928.0	1928.8	11.0	9.5	1.1	0.9	0.44
All Cases vs. All ARSD Controls	1928.0	1929.2	11.0	10.3	1.1	1.0	0.07
Company A							
All Cases vs. All Controls	1930.1	1931.6	10.3	7.2	1.4	1.0	0.17
- Cases vs. ARS Controls	1930.1	1931.3	10.3	8.5	1.4	1.2	0.48
- Cases vs. ARSD Controls	1930.1	1932.3	10.3	8.8	1.4	1.2	0.015
Company B							
All Cases vs. All Controls	1925.8	1926.1	11.3	9.3	1.6	1.3	0.78
- Cases vs. ARS Controls	1925.8	1926.3	11.3	9.8	1.6	1.4	0.72
- Cases vs. ARSD Controls	1925.8	1926.1	11.3	10.9	1.6	1.5	0.73
<u>Confirmed Cases</u>							
All Cases vs. All Controls	1928.4	1929.6	10.4	9.3	1.3	1.2	0.20
COMP A Cases vs. Controls	1930.4	1932.5	9.5	7.3	1.7	1.3	0.10
COMP B Cases vs. Controls	1926.3	1926.5	11.1	10.3	2.0	1.8	0.87

TABLE 42 (cont'd)

PAIRED T-TESTS FOR YEAR OF HIRE - cont. p. 2

	<u>Mean</u>		<u>S.D.</u>		<u>S.E.</u>		<u>Two-Tailed</u>
	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Probability</u>
<u>Unconfirmed Cases</u>							
All Cases vs. All Controls	1927.3	1927.8	12.0	7.7	2.0	1.2	0.72
COMP A Cases vs. Controls	1929.6	1930.3	12.0	7.0	2.7	1.6	0.78
COMB B Cases vs. Controls	1925.0	1925.4	12.0	7.8	2.8	1.8	0.82

TABLE 43

FIRST CALENDAR YEAR IN THE INDUSTRY, BY PATHOLOGY

I. CONFIRMED CASES VS. MATCHED CONTROL

CONFIRMED CASES AND MATCHED CONTROLS

<u>Calendar Year</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
1910-1919	16	25	62	25
1920-1929	27	42	86	34
1930-1939	3	5	20	8
1940-1949	17	27	72	29
1950-1959	<u>1</u>	<u>2</u>	<u>9</u>	<u>4</u>
Totals	64	100	249	100

TABLE 44

FIRST CALENDAR YEAR IN THE INDUSTRY, BY PATHOLOGY

II. UNCONFIRMED CASES VS. MATCHED CONTROLS

<u>Calendar Year</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
1910-1919	16	42	34	24
1920-1929	10	26	63	44
1930-1939	-	-	7	5
1940-1949	11	30	38	26
1950-1959	<u>1</u>	<u>3</u>	<u>2</u>	<u>1</u>
Totals	38	100	144	100

TABLE 45

CHARACTERISTICS OF COMPANY A SUBJECTS WHO ENTERED THE
INDUSTRY DURING AND AFTER THE FIRST DECADE, COMPARED
WITH APPROPRIATE CONTROLS

	<u>Mean</u>	<u>S.E.</u>	<u>S.D.</u>	<u>Median</u>	<u>Mode</u>
Decade 1910-1919					
1. Cases					
Total Duration	385	35	117	420	167
Age at Hire	25.5	1.2	4.0	25.2	22
Age at Death	76.8	1.3	4.3	77.0	73
2. ARSD Controls					
Total Duration	317	38	126	336	88
Age at Hire	34.4	2.6	8.5	33	24.5
Decade 1920 +					
1. Cases					
Total Duration	325	19	120	332	318
Age at Hire	32.9	1.9	12.1	31	19
Age at Death	68.7	1.5	9.7	69.7	68
2. ARSD Controls					
Total Duration	321	17	107	354	150
Age at Hire	33.5	1.6	10.5	31.1	22.0

TABLE 46

T-TESTS FOR GROUP HIRED DURING FIRST DECADE, BY PATHOLOGY

COMPARISON	<u>Mean</u>		<u>S.D.</u>		<u>S.E.</u>		<u>Two-Tailed Probability</u>
	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	
Comp A Cases vs. ARSD Controls							
1. Total Duration	338	320	121	110	17	15	0.09
2. Age at Hire	31.4	33.5	11.2	10.0	1.6	1.4	0.02
3. Year of Hire	1930.1	1932.3	10.3	8.8	1.4	1.2	0.015
First Decade Cases vs. ARSD Controls							
1. Total Duration	385	317	117	126	35	38	0.078
2. Age at Hire	25.5	34.4	4.0	8.5	1.2	2.6	0.006
3. Year of Hire	1917.1	1926.9	2.0	7.2	0.6	2.2	0.002
<u>Confirmed</u>							
1. Total Duration	326	280	150	116	67	52	0.396
2. Age at Hire	24.6	35.0	1.7	4.8	0.7	2.1	0.014
3. Year of Hire	1916.8	1929.1	2.7	3.4	1.2	1.5	0.007
<u>Unconfirmed</u>							
1. Total Duration	434	347	53	137	22	56	0.156
2. Age at Hire	26.3	33.9	5.4	11.1	2.2	4.6	0.145
3. Year of Hire	1917.3	1925.1	1.5	9.3	0.6	3.8	0.095

TABLE 46 (cont'd)

T-TESTS FOR GROUP HIRED DURING FIRST DECADE, BY PATHOLOGY - cont. p. 2

	<u>Mean</u>		<u>S.D.</u>		<u>S.E.</u>		<u>Two-Tailed</u>
	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Probability</u>
Later Decade Cases vs. ARSD Controls							
1. Total Duration	325	321	120	107	19	17	0.643
2. Age at Hire	32.9	33.5	12.1	10.6	1.9	1.7	0.365
3. Year of Hire	1933.6	1934.0	8.6	8.6	1.4	1.4	0.557

TABLE 47

TOTAL DURATION OF EMPLOYMENT (IN MONTHS) IN ACTIVE OTs

1. COMPANY A CASES VS. CONTROLS

<u>Total Duration</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
<149	3	5.7	16	8.0
150-199	8	15.4	14	7.1
200-249	4	7.7	17	8.6
250-299	4	7.7	31	15.7
300-349	6	11.5	32	16.2
350-399	6	11.5	35	17.8
400-449	9	17.3	23	11.7
450-499	9	17.3	20	10.1
>499	<u>3</u>	<u>5.8</u>	<u>9</u>	<u>4.6</u>
Totals	52	100.0	197	100.0

Mean	337.7	325.0
Median	351.5	331.4
S.D.	120.9	110.9
S.E.	16.8	7.9

TABLE 48

TOTAL DURATION OF EMPLOYMENT (IN MONTHS) IN ACTIVE OTs
2. COMPANY B CASES VS. CONTROLS

<u>Total Duration</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
< 149	1	2.0	2	1.0
150-199	3	6.0	13	6.7
200-249	3	6.0	14	7.2
250-299	8	16.0	23	11.7
300-349	3	6.0	14	7.2
350-399	5	10.0	36	18.4
400-449	12	24.0	28	14.3
450-499	7	14.0	39	19.9
> 499	<u>8</u>	<u>16.0</u>	<u>27</u>	<u>13.8</u>
Totals	50	100.0	196	100.0

Mean	380.0	380.5
Median	406.5	394.5
S.D.	113.2	112.1
S.E.	16.0	8.0

TABLE 49

TOTAL DURATION OF EMPLOYMENT (IN MONTHS) IN ACTIVE OTs

3. ALL CASES VS. ALL CONTROLS

<u>Total Duration</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
< 149	4	4.0	18	4.7
150-199	11	10.8	27	6.9
200-249	7	6.9	31	7.9
250-299	12	11.7	54	13.8
300-349	9	8.8	46	11.7
350-399	11	10.8	71	18.1
400-449	21	20.6	51	13.0
450-499	16	15.7	59	15.0
> 499	<u>11</u>	<u>10.8</u>	<u>36</u>	<u>9.2</u>
Totals	102	100.0	393	100.0

Mean	358.5	352.7
Median	385.5	369.3
S.D.	118.6	114.8
S.E.	11.7	5.8

TABLE 50

TOTAL DURATION OF EMPLOYMENT (IN ACTIVE OTs) BY PATHOLOGY

I. CONFIRMED CASES VS. MATCHED CONTROLS

<u>Total Duration</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
<149	1	2	10	4
150-199	8	13	13	5
200-249	4	6	22	9
250-299	8	13	34	14
300-349	6	9	28	11
350-399	3	5	45	18
400-449	14	22	34	14
450-499	12	19	34	14
500+	<u>8</u>	<u>13</u>	<u>29</u>	<u>12</u>
Totals	64	100	249	100

Mean

368

360

TABLE 51

TOTAL DURATION OF EMPLOYMENT (IN ACTIVE OTs), BY PATHOLOGY

II. UNCONFIRMED CASES VS. MATCHED CONTROLS

<u>Total Duration</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
<149	3	8	8	6
150-199	3	8	14	10
200-249	3	8	9	6
250-299	4	10	20	14
300-349	3	8	18	12
350-399	8	21	26	18
400-449	7	18	17	12
450-499	4	10	25	17
500+	<u>3</u>	<u>8</u>	<u>7</u>	<u>5</u>
Totals	38	100	144	100

Mean

342

342

TABLE 52

PAIRED T-TESTS FOR DURATION IN ACTIVE OTs

<u>OVERALL</u>							
COMPARISON	<u>Mean</u>		<u>S.D.</u>		<u>S.E.</u>		<u>Two-Tailed Probability</u>
	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	
All Cases vs. All Controls	358	353	118	76	12	8	0.54
All Cases vs. All ARS Controls	358	357	118	88	12	9	0.94
All Cases vs. All ARSD Controls	358	350	118	109	12	11	0.24
Company A							
All Cases vs. All Controls	338	326	121	75	17	10	0.38
- Cases vs. ARS Controls	338	335	121	87	16	12	0.90
- Cases vs. ARSD Controls	338	320	121	110	17	15	0.09
Company B							
All Cases vs. All Controls	380	381	113	67	16	10	0.96
- Cases vs. ARS Controls	380	380	113	83	16	12	0.98
- Cases vs. ARSD Controls	380	382	113	100	16	14	0.88
<u>Confirmed Cases</u>							
All Cases vs. All Controls	368	360	119	77	15	10	0.39
COMP A Cases vs. Controls	344	331	124	73	22	13	0.35
COMP B Cases vs. Controls	394	391	111	69	20	12	0.82

TABLE 52 (cont'd)

PAIRED T-TESTS FOR DURATION IN ACTIVE OTs - cont. pg. 2

	<u>Mean</u>		<u>S.D.</u>		<u>S.E.</u>		<u>Two-Tailed Probability</u>
	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	
<u>Unconfirmed Cases</u>							
All Cases vs. All Controls	342	341	117	74	19	12	0.96
COMP A Cases vs. Controls	327	319	118	79	27	18	0.76
COMP B Cases vs. Controls	358	364	117	62	27	14	0.81

TABLE 53

AGE AT HIRE

2. COMPANY B CASES VS. CONTROLS

<u>Age at Hire</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
15-19	7	14.0	21	10.7
20-24	15	30.0	61	31.1
25-29	12	24.0	38	19.4
30-34	7	14.0	21	10.7
35-39	3	6.0	28	14.3
40-44	1	2.0	14	7.1
45-49	2	4.0	8	4.1
50-54	2	4.0	4	2.0
>54	<u>1</u>	<u>2.0</u>	<u>1</u>	<u>0.5</u>
Totals	50	100.0	196	100.0

Mean	28.1	28.8
Median	25.5	26.6
S.D.	9.6	9.0
S.E.	1.4	0.6

TABLE 54

AGE AT HIRE

1. COMPANY A CASES VS. CONTROLS

<u>Age at Hire</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
15-19	6	11.5	8	4.1
20-24	12	23.1	39	19.8
25-29	11	21.2	34	17.3
30-34	7	13.5	36	18.3
35-39	3	5.8	24	12.2
40-44	4	7.7	22	11.2
45-49	4	7.7	14	17.1
50-54	4	7.7	14	17.1
>54	<u>1</u>	<u>1.9</u>	<u>6</u>	<u>3.0</u>
Totals	52	100.0	197	100.0

Mean	31.4	33.4
Median	27.5	31.6
S.D.	11.2	10.4
S.E.	1.6	0.7

TABLE 55

AGE AT HIRE

3. ALL CASES VS. ALL CONTROLS

Age at Hire	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
15-19	13	12.7	29	7.4
20-24	27	26.5	100	25.4
25-29	23	22.5	72	18.3
30-34	14	13.7	57	14.5
35-39	6	5.9	52	13.2
40-44	5	4.9	36	9.2
45-49	6	5.9	22	5.6
50-54	6	5.9	18	4.6
>54	<u>2</u>	<u>2.0</u>	<u>7</u>	<u>1.8</u>
Totals	102	100.0	393	100.0

Mean	29.8	31.1
Median	26.8	29.1
S.D.	10.5	10.0
S.E.	1.04	0.5

TABLE 56

AGE AT HIRE, BY PATHOLOGY

I. CONFIRMED CASES VS. MATCHED CONTROLS

<u>Age at Hire</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
15-19	8	12	20	8
20-24	15	23	61	24
25-29	19	30	43	17
30-34	6	9	34	14
35-39	4	6	35	14
40-44	4	6	30	12
45-49	4	6	13	5
50-54	3	5	11	4
>54	<u>1</u>	<u>2</u>	<u>2</u>	<u>1</u>
Totals	64	100	249	100

TABLE 57

AGE AT HIRE, BY PATHOLOGY

II. UNCONFIRMED CASES VS. MATCHED CONTROLS

<u>Age at Hire</u>	<u>Cases</u>		<u>Controls</u>	
	<u>Frequency</u>	<u>Per Cent</u>	<u>Frequency</u>	<u>Per Cent</u>
15-19	5	13	9	6
20-24	12	32	39	27
25-29	4	11	29	20
30-34	8	21	23	16
35-39	2	5	17	12
40-44	1	3	6	4
45-49	2	5	9	6
50-54	3	8	7	5
>55	<u>1</u>	3	<u>5</u>	3
Totals	38		144	

Mean

30.2

31.1

TABLE 58

PAIRED T-TESTS FOR AGE AT HIRE

<u>OVERALL</u>							
COMPARISON	<u>Mean</u>		<u>S.D.</u>		<u>S.E.</u>		Two-Tailed Probability
	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	
All Cases vs. All Controls	29.8	30.1	10.5	7.1	1.0	0.7	0.26
All Cases vs. All ARS Controls	29.8	30.5	10.5	7.8	1.0	0.8	0.49
All Cases vs. All ARSD Controls	29.8	31.0	10.5	9.2	1.0	0.9	0.07
Company A							
All Cases vs. All Controls	31.4	32.9	11.2	7.6	1.6	1.1	0.18
- Cases vs. ARS Controls	31.4	32.5	11.2	8.1	1.6	1.1	0.49
- Cases vs. ARSD Controls	31.4	33.5	11.2	10.0	1.6	1.4	0.02
Company B							
All Cases vs. All Controls	28.1	28.4	9.6	5.7	1.4	0.8	0.84
- Cases vs. ARS Controls	28.1	28.5	9.6	6.9	1.4	1.0	0.81
- Cases vs. ARSD Controls	28.1	28.5	9.6	7.6	1.4	1.0	0.73
<u>Confirmed Cases</u>							
All Cases vs. All Controls	29.6	30.6	10.2	7.3	1.3	0.9	0.24
COMP A Cases vs. Controls	31.1	33.0	11.4	7.4	2.0	1.3	0.14
COMP B Cases vs. Controls	28.0	28.1	8.8	6.4	1.6	1.1	0.88

TABLE 58 (cont'd)

PAIRED T-TESTS FOR AGE AT HIRE - cont. pg. 2

	<u>Mean</u>		<u>S.D.</u>		<u>S.E.</u>		<u>Two-Tailed Probability</u>
	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	<u>Cases</u>	<u>Controls</u>	
<u>Unconfirmed Cases</u>							
All Cases vs. All Controls	30.2	30.8	11.2	6.8	1.8	1.1	0.69
COMP A Cases vs. Controls	31.9	32.8	11.3	8.1	2.6	1.9	0.68
COMP B Cases vs. Controls	28.4	28.7	11.1	4.7	2.5	1.1	0.89

ANALYSIS II: OCCUPATIONAL EXPOSURE

This second of two analysis chapters will present the findings relating specifically to occupational exposures and will utilize the OT and OTG System used previously in other OHSG studies. Because the differences between cases and control, in total duration of employment within active OTs were not statistically significant, the analysis of control work histories will not be terminated at the point where the control attained the duration of the case, as was stipulated during the earlier description of the design for this study. Also, because there was no statistically significant difference in duration within active OTs between ARS- and ARSD-matched controls, this dichotomy will be essentially ignored during the following discussion.

Most Representative OTGs

Before the calculation of odds ratios for specific OTGs, it would be useful to view the work history data in a general manner, for which purpose Tables 59 and 62 present the first and second most representative OTGs, defined as those OTGs in which subjects spent the longest and second largest periods of time, for both cases and controls in each company separately and combined. Among Company A cases, the five most representative OTGs are general services, fabrication of tires and beads, batch preparation, curing, and metal handling, while controls had general services, chemicals, fabrication, maintenance, and three OTGs tied for fifth, as their most representative OTGs. Among Company B subjects, the most representative OTGs for cases were Maintenance, fabrication,

general services and batch preparation, while among controls the MROTGs were maintenance, fabrication, general services, batch preparation, and calendering. Among Company A subjects, therefore, two of the five MROTGs were shared in common by cases and controls, while among Company B subjects, four were shared in common. We then calculated odds ratios and chi squares for each of these OTGs and did not find any significant elevations for MROTGs and observed only two second MROTGs (Batch Prep, Inspection, Prep Other) in Company B with significantly elevated ORs.

Standard OTG Analyses

The data were first examined according to the standard OTG classification, used in numerous other OHSR reports, a classification which includes twenty-one OTGs (See Appendix I for a description of the industrial processes included in the OTGs which comprise them), based on similar production processes and materials, but not necessarily based on similar exposures. For this reason, analyses were also performed on chemical-specific OTGs created especially for the suspect gastric carcinogens in this investigation.

The Odds Ratios for the standard OTGs were examined in numerous ways, each addressing a different question, with each examination being equivalent to stratification on the factor under examination, a procedure which controls for confounding. In all, we examined the odds ratios according to control group (ARS and ARSD), pathology confirmation status, year of hire, birthplace, age at hire and age at death, in addition to the chemical specific analyses, with many of these stratifications including four different exposure times:

ever, two years, five years, and ten years - each of which were compared with no exposure. The results of these analyses are presented in Tables 63 to 95. It should be noted, before examining these tables, that one or two asterisks indicate the p-value (two-tailed) for a test of significance of the odds ratios being different from unity. The test statistic (CHI) is an approximate standard normal variate. In addition, the ninety percent confidence interval is presented, along with the numbers of exposed and unexposed cases and controls.

Examination of the first seven tables, which present the overall and company and control group specific odds ratios on an ever-never exposure basis, reveals not a single significantly elevated odds ratio, although the ORs for calendering, tuber, and cure preparation were somewhat elevated for comparisons with one or the other control group within Company A. In Company B, on the other hand, the OR for calendering was twice statistically significantly lower than unity.

This first set of analyses of the data, examining exposure on an ever-never basis, was followed by further examination on the basis of two, five, and ten years of exposure within each of these OTGs, all compared with no exposure at all. Each of these analyses was performed separately for each company (Tables 70 to 75) and only one OR - Calendering among Company B subjects in the comparison of two years of exposure versus none - was statistically significantly elevated, while Fabrication appeared elevated twice in this sequence of analyses.

When these analyses were further stratified according to pathology confirmation status, the following significantly elevated ratios, with a considerable number of exposed cases, were observed: among confirmed cases - metals for two or more years in Company A (OR = 2.30 with 14

exposed cases) Fabrication for both two (OR = 3.1 with 8 exposed cases) and five or more years (OR = 3.5 with 7 or more cases) in Company A and among unconfirmed cases - none.

We then stratified subjects according to their pathology confirmation status (Tables 76 and 77), analyzing separately confirmed and unconfirmed cases and their matched controls, on the assumption that there may be "contamination" by non-stomach cancer cases among the unconfirmed group. This analysis indicated two elevated ORs - for curing and Prep -Other, both of which occurred among the unconfirmed cases.

The next analysis was based on the age at hire of the case, which was dichotomized according to whether the case began work in the industry either before or after the age of twenty-four. The attempt here was to separate those for whom the exposure began at a young age compared with those whose exposure began at an older age, and the results of these analyses are presented in Tables 78 to 83. Among the younger group overall, we observed elevated odds ratios for Fabrication and Cure Preparation, with cases in Company B statistically associated for the overall elevation. Within this company, the odds ratios for Curing and Prep. - Other, were slightly, although not statistically significantly, elevated as well. Among Company A subjects exposed at younger ages, on the other hand, there was a significant elevation for Calendering and non-significantly elevated ORs for Tuber, Cureprep, Curing, and Chemicals, although the number of exposed cases, in all of these instances, was small. Similar analyses for individuals whose first exposure occurred at an older age did not reveal any elevated ratios at all. Since the groupings for age at hire

are based on the values for the case, when the matched analyses are conducted the age at hire for the controls can take on any value. Accordingly, we dissolved the matching and calculated unmatched odds ratios but did not observe any significant elevations.

We next looked separately at cases, and their matched controls, who died before and after the age of sixty-five (Tables 84-87) since it has been postulated that these may be two distinct entities with different causal mechanisms, one among young cases and the other among the older ones. There were a few elevated ORs among those who died at younger ages - Curing, General Service, Final Inspection, Calendering, and Chemicals - in Company A, and none among this same group in Company B. Among those who died at older ages in Company A, on the other hand, there were no significant elevations, although Tubers was somewhat high. Among subjects in Company B, once again, we found nothing of interest.

For the analysis based on birthplace and decade of hire, we dissolved the matching for reasons stated earlier. For the former, the only significant elevated odds ratios were found for the Calendering and Tuber OTGs among native born employees at Company A, where the ratios were each 2.6, with 9 and 11 exposed cases, respectively. For the decade of hire analysis, separate odds ratios and CHIS were calculated for each of the OTGs for five decades (1910-1959), in each Company separately. The only significant finding was that for both Company A and B, the odds ratios were high (5.6 and 4.0) for cases in Fabrication who entered the industry during the first decade. For the 11 Company A cases in this group, 5 were exposed, while 15 of 21 cases in Company B had been employed in the Fabrication OTG.

The next series of analyses examined the odds ratios for those OTs judged to have potential for exposures to four specific chemicals or classes - polycyclic hydrocarbons, nitrosamines, carbon black, and asbestos or asbestos containing talc. Three environmental scientists at OHSG, whose responsibilities include detailed studies of the occupational environment of workers at the two companies under study, were asked to independently rate each of the OTs according to the exposure level-high, moderate, low, or none - for each of the four chemicals under study. Since this was an ordinal-level assessment (high, moderate, low or none), the numerical values of three, two, one and zero were assigned to these levels, and an average of all three judges was then calculated for each OT (see Appendix III for inter-observer reliability). After these means had been calculated, cut-off points for each type of exposure were established, after which we had groups of OTs considered to have high, moderate, low, or no worker potential for exposure to the four chemicals under investigation and a listing of these groups is presented in Table 98. Because those judgements were subjective, we first analyzed the high groups compared with all others, and we then combined the high and moderate group and compared those against the remainder, the former always being considered exposed while the latter was considered unexposed. Each of those analyses was performed, in addition, for the four exposure-time groups of ever-never and two, five, and ten years versus none, and the results are presented in Tables 88 to 95. Examination of these results indicates the following: no elevated odds ratios in either company for the aromatic hydrocarbons; a slightly but significantly elevated OR for Company B subjects exposed for five or more years to high levels of

nitrosamines (OR = 1.7) with non-significant elevations for Company B subjects as well; slightly elevated ratios for exposure to carbon black among Company A and B subjects, although none were statistically significant; and statistically significantly elevated odds ratios for Company A subjects exposed to high or moderate levels of asbestos, while Company B subjects had significantly low ratios for exposure to this same chemical. These low ratios among Company B subjects, however, were found only for the combined high or moderate exposures. When moderate exposure was compared against all others (including high), we observed slightly elevated ORs even in Company B.

When these chemical specific analyses were further stratified according to pathology, there were no significantly high ratios among confirmed cases in either company for any of the chemicals. Among unconfirmed cases, on the other hand, we found high odds ratios for numerous combinations of asbestos exposure, as well as for numerous time and exposure categories of polycyclic hydrocarbons, nitrosamines, and carbon black, with all significant elevations occurring within Company A. It should be kept in mind when considering these findings, however, that there were only sixteen (31 percent) unconfirmed cases among the fifty-two total cases in Company A.

Because of the finding of elevated odds ratios for asbestos exposure among Company A subjects, and because of the large number of potentially exposed subjects (27), additional attention was directed towards this category. We next performed a paired T-Test and found that Company A cases averaged approximately four years (49 months) in OTs judged to have potentially high asbestos exposure, while their matched controls averaged half that exposure time (25 months). Using

a one-tailed probability test of significance, this difference was statistically significant at the five percent level. A similar analysis among Company B subjects revealed no significant differences between cases and comparands, as we expected from the absence of significant odds ratios for this chemical, although subjects in this company spent slightly more time in high asbestos exposure OTs (eighty-four months for cases and eighty for controls) than did the subjects in Company A.

After this finding, two groups of Company A cases were further examined - those who entered before and after 1920, since we had earlier found a disproportionate number of cases among the former. Paired T-Tests revealed that the eleven early entry cases averaged 82 months in areas with potentially high asbestos exposure, with their matched controls averaging 24.5 months, while the respective findings for the 41 later entry cases and their matched controls were 40 and 26 months, with neither of these differences achieving statistical significance. When exposure differences among the early entry group was further analyzed separately for ARS- and ARSD-matched controls, the cases again averaged 82 months, of course, while controls averaged 35 and 12 months, respectively. The overall significant difference in potential asbestos exposure, therefore, appears to be statistically accounted for by the differences between early entry cases and their matched controls.

These analyses were further pursued by the calculation of unmatched odds ratios for potential asbestos exposure for each decade of entry, and the results of these calculations are presented in Table 96, from which we see that only for the second decade was the odds

ratio significantly elevated, although there was a non-significant elevation for the first decade as well. Of the 32 cases who entered during the first decade, fully half had been exposed with 30 of the 73 controls having similar experiences, while 7 of the twenty cases and 21 of the 74 controls who entered in 1930 or later had worked in areas with potentially high asbestos exposures. It is interesting to note here that the similar matched analysis described elsewhere in this chapter, which utilized standard OTGs, did not indicate any consistent excesses.

Because these earlier entry odds ratios were found to be elevated, we next examined the distributions of total time spent in potentially high asbestos OTs only for those individuals who had ever worked in these areas and who entered the industry before 1930. The cases in this group averaged 81.3 months in these OTs while controls had a mean of 66.8. For subjects entering in 1930 or later, the mean duration in potentially high asbestos exposure areas was 48.9 months while controls averaged 70.8.

The final analysis in this series examined the odds ratios, and related factors for different latency periods, beginning with 40 years. These latency periods are calculated by subtracting the year of hire from the year of death, although the reader should recall that most controls were still alive on 1/1/76, although this date was used as the 'year of death' in these calculations. Based on this determination of latency period, we observe a statistically significantly elevated odds ratio of 2.24 for potential asbestos exposure among cases, compared with controls who had the same potential latency period. The results of this analysis are presented in Table 97. The results of both the potential latency and calendar year of entry analyses are summarized in

Table 99.

This analysis was followed by one which examined the calendar periods during which the two groups in Company A actually worked in these high risk OTs, and the frequency distributions revealed that approximately fifty percent of the case instances of employment within these OTs had occurred by the year 1940, while only thirty percent of the control instances had occurred by this date. Although this finding indicates that the exposures occurred well before the disease, we further examined the T-Test for cases who died before and after the age of seventy. Since retirement is mandatory by the age of sixty-five, any exposures among those who died after the age of seventy must have occurred at least five years prior to death, a time frame which can be considered well within the latency period. Among Company A subjects, the results indicate that the difference in asbestos exposure between cases and controls was even greater among those dying at older ages (fifty-four versus twenty-one months), a finding which strengthens our confidence that exposures may have occurred enough earlier than the disease to have had an impact, with a reasonably long latency period.

TABLE 59

MOST REPRESENTATIVE OTGs (MROTGs) FOR COMPANY A

OTG	<u>CONTROLS</u> CUM			χ^2	OR	<u>CASES</u> CUM		
	%	%	N			%	%	N
GENERAL SERVICE	15	15	30	0.01	1.0	15	15	8
CHEMICALS	13	28	25	5.10	0.1	2	17	1
FABRICATION	10	38	19	0.64	1.5	13	30	7
MAINTENANCE	10	48	19	0.77	0.6	6	36	3
CALENDER	7	55	14	0.02	1.1	8	44	4
CURING	6	61	13	0.56	1.5	9	53	5
MILLING	7	68	14	0.73	0.5	4	57	2
METAL HANDLING	6	74	11	1.11	1.8	9	66	5
BATCH PREP.	5	79	10	1.50	2.0	9	75	5
INSPECTION	5	84	10	0.04	1.1	6	81	3
RECLAIM	4	88	9	0.05	0.8	4	85	2
SHIP. & REC.	3	91	6	0.08	1.3	4	89	2
TUBER	3	94	6	0.88	2.0	6	95	3
FIN. INSPECT.	1	95	3	-	-	-	95	-
TUBES-FABRIC	1	96	3	1.13	2.6	4	99	2
UNKNOWN	1	97	3	-	-	-	99	-
CURE PREP.	1	98	2	-	-	-	99	-
OTHER RUBBER	-	98	-	-	-	-	99	-
PLASTICS	-	98	-	-	-	-	99	-
PREP. OTHER	-	98	-	-	-	-	99	-
SALARY	-	98	-	-	-	-	99	-
<u>TOTALS</u>		98	197				99	52

TABLE 60

SECOND MOST REPRESENTATIVE OTGs FOR COMPANY A

OTG	CONTROLS			χ^2	OR	CASES		
	%	%	N			%	%	N
GENERAL SERVICE	9	9	17	0.46	0.6	6	6	3
CHEMICALS	8	17	16	2.5	2.1	15	21	8
MAINTENANCE	8	25	16	0.01	0.9	7	28	4
UNKNOWN	8	33	16	0.01	0.9	7	35	4
BATCH PREP.	6	39	12	0.39	0.6	4	39	2
MILLING	6	45	12	0.39	0.6	4	43	2
CALENDER	4	49	9	0.81	1.7	7	50	4
CURING	4	53	9	0.13	1.3	6	56	3
RECLAIM	4	57	9	-	-	-	56	-
TUBES	4	61	9	0.13	1.3	6	62	3
CURE PREP.	4	65	8	0.28	1.4	6	68	3
FABRICATION	4	69	8	4.34	3.1	11	79	6
INSPECTION	4	73	8	0.54	0.5	2	81	1
SHIP. & REC.	4	77	8	0.54	0.5	2	83	1
METAL HANDLING	2	79	5	0.26	1.5	4	87	2
TUBER	2	81	4	0.58	1.9	4	91	2
OTHER RUBBER	1	82	1	-	-	-	91	-
PREP. OTHER	1	83	1	-	-	-	91	-
FINAL INSPECT.	-	-	-	-	-	-	91	-
PLASTICS	-	-	-	-	-	-	91	-
SALARY	-	-	-	-	-	-	91	-
NO. 2nd MROT	15	98	29	-	-	7	98	4
<u>TOTALS</u>		98	197				98	52

TABLE 61

MOST REPRESENTATIVE OTGs FOR COMPANY B

OTG	CONTROLS			χ^2	OR	CASES		
	%	CUM %	N			%	CUM %	N
MAINTENANCE	19	19	38	0.05	0.9	18	18	9
FABRICATION	11	30	21	0.43	1.4	14	32	7
GENERAL SERVICE	11	41	21	0.07	1.1	12	44	6
BATCH PREP.	9	50	18	0.03	1.1	10	54	5
CALENDER	9	59	18	0.52	0.6	6	60	3
CURING	6	65	12	1.35	0.3	2	62	1
TUBES-FABR.	6	71	12	0.33	0.6	4	66	2
CURE PREP.	<1	71	1	1.1	4.0	2	68	1
INSPECTION	5	76	9	0.03	0.9	4	72	2
PREP. OTHER	5	81	10	0.06	1.2	6	78	3
TUBER	<1	81	1	-	-	-	78	-
PLASTICS	4	85	8	0.01	1.0	4	82	2
SHIP. & REC.	4	89	7	0.60	1.7	6	88	3
UNKNOWN	4	93	7	0.02	1.1	4	92	2
FINAL INSPECT.	1	94	3	1.22	2.7	4	96	2
METAL HANDLING	1	95	3	0.05	1.3	2	98	1
MILLING	1	96	2	0.3	2.0	2	100	1
OTHER RUBBER	1	97	3	-	-	-	100	-
CHEMICALS	<1	97	1	-	-	-	100	-
RECLAIM	<1	97	1	-	-	-	100	-
SALARY	-	97	-	-	-	-	100	-
<u>TOTALS</u>		97	196				100	50

TABLE 62

SECOND MOST REPRESENTATIVE OTGs FOR COMPANY B

OTG	CONTROLS			X ²	OR	CASES		
	%	CUM %	N			%	CUM %	N
GENERAL SERVICE	15	15	29	2.7	0.4	6	6	3
TUBES	10	25	20	3.4	0.2	2	8	1
CALENDER	8	33	16	-	-	-	8	-
MAINTENANCE	7	40	13	0.03	0.9	6	14	3
BATCH PREP.	6	46	11	4.13	2.7	14	28	7
FINAL INSPECT.	5	51	9	0.17	1.3	6	34	3
CURE PREP.	4	55	7	-	-	-	34	-
FABRICATION	4	59	8	1.32	2.1	8	42	4
INSPECTION	4	63	7	5.65	3.7	12	54	6
UNKNOWN	4	67	7	0.60	1.7	6	60	3
CURING	3	70	6	-	-	-	60	-
PLASTICS	3	73	6	-	-	-	60	-
PREP. OTHER	2	75	5	8.33	5.2	12	72	6
RECLAIM	2	77	5	0.05	0.8	2	74	1
SHIP. & REC.	3	80	6	-	-	-	74	-
CHEMICALS	1	81	3	-	-	-	74	-
MILLING	2	83	4	-	-	-	74	-
OTHER RUBBER	2	85	4	2.26	3.0	6	80	3
TUBER	1	86	3	1.22	2.7	4	84	2
METAL HANDLING	1	87	2	-	-	-	84	-
SALARY	-	87	-	-	-	-	84	-
NO. 2 nd MROT	13	100	25	-	-	16	100	8
<u>TOTALS</u>		100	196				100	50

TABLE 63

ODDS RATIOS FOR ALL CASES COMPARED WITH ALL THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	27	75	81	312	1.42		1.48	0.94	2.23
2. MILLING	8	94	49	344	1.48		0.52	0.25	1.08
3. CALENDER	25	77	114	279	0.99		0.78	0.52	1.18
4. TUBER	17	85	59	334	0.36		1.12	0.70	1.79
5. FABRICATION	36	66	119	274	0.99		1.29	0.84	1.97
6. TUBES-FABRICATION	25	77	103	290	0.33		0.92	0.60	1.40
7. CURE PREPARATION	17	85	49	344	1.22		1.43	0.88	2.32
8. CURING	30	72	99	294	0.75		1.20	0.81	1.77
9. INSPECTION	22	80	90	303	0.25		0.92	0.56	1.53
10. MAINTENANCE	28	74	90	303	0.90		1.27	0.82	1.97
11. GENERAL SERVICE	42	60	168	225	0.18		0.96	0.66	1.40
12. SHIP. & REC.	16	86	58	335	0.27		1.09	0.64	1.81
13. RECLAIM	10	92	48	345	0.68		0.79	0.44	1.41
14. CHEMICALS	4	98	20	373	0.48		0.76	0.30	1.93
15. PLASTICS	5	97	36	357	1.47		0.44	0.18	1.10
16. PREP. - OTHER	24	78	67	326	1.42		1.46	0.94	2.28
17. FINAL INSPECTION	15	87	56	337	0.11		1.04	0.60	1.79
18. METAL HANDLING	28	74	99	294	0.49		1.16	0.71	1.87
19. OTHER RUBBER	8	94	47	346	0.18		0.60	0.29	1.22
20. SALARY	4	98	18	375	0.22		0.88	0.35	2.25
21. UNKNOWN	15	87	65	328	0.14		0.95	0.55	1.66

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 64

ODDS RATIOS FOR COMPANY A CASES COMPARED WITH ALL THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	11	41	28	169	1.46		1.91	0.92	3.96
2. MILLING	7	45	28	169	0.27		0.86	0.35	2.11
3. CALENDER	13	39	37	160	0.96		1.41	0.78	2.53
4. TUBER	11	41	24	173	1.58		1.81	0.98	3.36
5. FABRICATION	15	37	42	155	1.12		1.52	0.82	2.81
6. TUBES -FABRICATION	12	40	36	161	0.81		1.36	0.73	2.56
7. CURE PREPARATION	8	44	18	179	1.48		1.98	0.93	4.25
8. CURING	14	38	44	153	0.81		1.34	0.74	2.40
9. INSPECTION	7	45	33	164	0.50		0.79	0.37	1.71
10. MAINTENANCE	13	39	43	154	0.60		1.25	0.68	2.27
11. GENERAL SERVICE	25	27	76	121	1.19		1.47	0.86	2.49
12. SHIP. & REC.	6	46	24	173	0.07		0.96	0.42	2.23
13. RECLAIM	4	48	29	168	1.33		0.50	0.21	1.18
14. CHEMICALS	4	48	7	190	1.37		2.41	0.84	6.95
15. PLASTICS	0	52	0	197	-		-	-	-
16. PREP. - OTHER	5	47	10	187	1.12		1.74	0.77	3.91
17. FINAL INSPECTION	5	47	12	185	0.80		1.58	0.61	4.11
18. METAL HANDLING	27	25	85	112	1.23		1.48	0.87	2.52
19. OTHER RUBBER	1	51	3	194	0.18		1.25	0.17	9.19
20. SALARY	2	50	16	181	0.98		0.47	0.15	1.67
21. UNKNOWN	18	42	33	164	0.55		1.27	0.62	2.63

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 65

ODDS RATIOS FOR COMPANY A CASES COMPARED WITH THEIR ARS-MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	11	41	13	88	1.64		2.50	1.00	6.26
2. MILLING	7	45	11	90	0.49		1.31	0.53	3.28
3. CALENDER	13	39	20	81	0.65		1.31	0.66	2.60
4. TUBER	11	41	14	87	1.00		1.48	0.78	2.83
5. FABRICATION	15	37	24	77	0.59		1.27	0.65	2.50
6. TUBES -FABRICATION	12	40	21	80	0.35		1.16	0.58	2.30
7. CURE PREPARATION	8	44	10	91	1.06		1.75	0.73	4.17
8. CURING	14	38	25	76	0.39		1.17	0.61	2.22
9. INSPECTION	7	45	19	82	0.75		0.69	0.30	1.56
10. MAINTENANCE	13	39	26	75	0.00		1.00	---	---
11. GENERAL SERVICE	25	27	38	63	1.18		1.54	0.85	2.80
12. SHIP. & REC.	6	46	14	87	0.33		0.85	0.37	1.93
13. RECLAIM	4	48	18	83	1.66		0.42	0.17	0.99
14. CHEMICALS	4	48	3	98	1.44		3.50	0.84	14.60
15. PLASTICS	0	52	0	101	---		---	---	---
16. PREP. - OTHER	5	47	5	96	0.88		1.67	0.64	4.32
17. FINAL INSPECTION	5	47	6	95	0.63		1.50	0.52	4.31
18. METAL HANDLING	27	25	37	64	1.82		1.86	1.06	3.26
19. OTHER RUBBER	1	51	2	99	0.20		0.75	0.07	7.99
20. SALARY	2	50	9	92	1.12		0.38	0.09	1.59
21. UNKNOWN	9	43	15	86	0.40		1.30	0.54	3.15

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 66

ODDS RATIOS FOR COMPANY A CASES COMPARED WITH THEIR ARSD-MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG.	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	11	41	15	81	1.02		1.59	0.76	3.35
2. MILLING	7	45	17	79	0.94		0.56	0.20	1.54
3. CALENDER	13	39	17	79	1.05		1.50	0.80	2.83
4. TUBER	11	41	10	86	1.82		2.38	1.09	5.19
5. FABRICATION	15	37	18	78	1.41		1.83	0.90	3.72
6. TUBES -FABRICATION	12	40	15	81	1.26		1.80	0.83	3.88
7. CURE PREPARATION	8	44	8	88	1.46		2.25	0.90	5.60
8. CURING	14	38	19	77	1.20		1.65	0.83	3.30
9. INSPECTION	7	45	14	82	0.08		0.96	0.42	2.18
10. MAINTENANCE	13	39	17	79	1.18		1.67	0.82	3.40
11. GENERAL SERVICE	25	27	38	58	1.02		1.44	0.80	2.57
12. SHIP. & REC.	6	46	10	86	0.20		1.13	0.41	3.13
13. RECLAIM	4	48	11	85	0.68		0.65	0.23	1.83
14. CHEMICALS	4	48	4	92	0.93		1.88	0.61	5.72
15. PLASTICS	0	52	0	96	---		---	---	---
16. PREP. - OTHER	5	47	5	91	1.34		2.25	0.83	6.11
17. FINAL INSPECTION	5	47	6	90	0.78		1.70	0.55	5.22
18. METAL HANDLING	27	25	48	48	0.48		1.19	0.65	2.17
19. OTHER RUBBER	1	51	1	95	0.50		2.00	0.20	19.56
20. SALARY	2	50	7	89	0.71		0.57	0.16	2.10
21. UNKNOWN	9	43	18	78	0.17		0.92	0.43	2.00

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 67

ODDS RATIOS FOR COMPANY B CASES COMPARED WITH ALL THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER.

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	16	34	53	143	0.68		1.27	0.71	2.27
2. MILLING	1	49	21	175	1.94		0.19	0.04	0.77
3. CALENDER	12	38	77	119	2.21	*	0.44	0.24	0.81
4. TUBER	6	44	35	161	0.98		0.64	0.30	1.36
5. FABRICATION	21	29	77	119	0.34		1.13	0.63	2.02
6. TUBES - FABRICATION	13	37	67	129	1.14		0.67	0.37	1.19
7. CURE PREPARATION	9	41	31	165	0.38		1.16	0.62	2.18
8. CURING	16	34	59	137	0.26		1.09	0.64	1.84
9. INSPECTION	15	35	57	139	0.09		1.04	0.54	2.01
10. MAINTENANCE	15	35	50	146	0.66		1.30	0.68	2.49
11. GENERAL SERVICE	18	32	90	106	1.47		0.61	0.35	1.06
12. SHIP, & REC.	10	40	34	162	0.41		1.17	0.62	2.23
13. RECLAIM	6	44	19	177	0.46		1.26	0.56	2.84
14. CHEMICALS	0	50	25	171	1.84		0.00	---	---
15. PLASTICS	5	45	36	160	1.47		0.44	0.18	1.10
16. PREP. - OTHER	19	31	24	172	1.03		1.39	0.82	2.34
17. FINAL INSPECTION	10	40	44	152	0.40		0.85	0.43	1.68
18. METAL HANDLING	1	49	20	176	1.51		0.27	0.07	1.12
19. OTHER RUBBER	7	43	44	152	1.31		0.54	0.25	1.17
20. SALARY	2	48	2	194	1.50		4.00	0.97	18.29
21. UNKNOWN	5	45	32	164	0.44		0.79	0.27	1.59

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 68

ODDS RATIOS FOR COMPANY B CASES COMPARED WITH THEIR ARS-MATCHED CONTROLS EXPOSURE = EVER-NEVER

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	16	34	23	75	1.25		1.69	0.85	3.38
2. MILLING	1	49	6	92	1.07		0.33	0.06	1.31
3. CALENDER	12	38	39	59	2.00	*	0.42	0.20	0.96
4. TUBER	6	44	19	79	1.08		0.59	0.26	1.32
5. FABRICATION	21	29	44	54	0.31		0.89	0.50	1.61
6. TUBES-FABRICATION	13	37	39	59	1.71		0.53	0.28	0.98
7. CURE PREPARATION	9	41	17	81	0.07		1.03	0.50	2.13
8. CURING	16	34	29	69	0.20		1.08	0.57	2.04
9. INSPECTION	15	35	30	68	0.14		0.94	0.45	1.97
10. MAINTENANCE	15	35	22	76	0.94		1.47	0.75	2.88
11. GENERAL SERVICE	18	32	50	48	1.71		0.56	0.32	0.98
12. SHIP. & REC.	10	40	20	78	0.07		0.97	0.50	1.90
13. RECLAIM	6	44	8	90	0.78		1.57	0.61	4.05
14. CHEMICALS	0	50	7	91	1.87		0.00	---	---
15. PLASTICS	5	45	19	79	1.46		0.47	0.20	1.10
16. PREP. - OTHER	19	31	30	68	0.80		1.34	0.73	2.46
17. FINAL INSPECTION	10	40	25	73	0.82		0.70	0.34	1.44
18. METAL HANDLING	1	49	9	89	1.65		0.22	0.05	1.00
19. OTHER RUBBER	7	43	27	71	1.77		0.44	0.20	0.94
20. SALARY	2	48	0	98	2.00	*	---	---	---
21. UNKNOWN	5	45	13	85	0.00		1.00	---	---

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 69

ODDS RATIOS FOR COMPANY B CASES COMPARED WITH THEIR ARSD-MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	16	34	30	68	0.125		1.05	0.57	1.94
2. MILLING	1	49	15	83	2.38		0.13	0.03	0.53
3. CALENDER	12	38	38	60	1.96	*	0.46	0.24	0.88
4. TUBER	6	44	16	82	0.64		0.71	0.30	1.63
5. FABRICATION	21	29	33	65	0.98		1.46	0.78	2.74
6. TUBES -FABRICATION	13	37	28	70	0.35		0.87	0.45	1.67
7. CURE PREPARATION	9	41	16	82	0.62		1.31	0.64	2.68
8. CURING	16	34	30	68	0.18		1.06	0.61	1.85
9. INSPECTION	15	35	27	71	0.34		1.16	0.57	2.34
10. MAINTENANCE	15	35	28	70	0.21		1.10	0.52	2.36
11. GENERAL SERVICE	18	32	42	56	0.89		0.71	0.37	1.34
12. SHIP. & REC.	10	40	14	84	0.93		1.54	0.71	3.35
13. RECLAIM	6	44	11	87	0.09		1.05	0.44	2.52
14. CHEMICALS	0	50	8	90	1.73		---	---	---
15. PLASTICS	5	45	17	81	1.41		0.38	0.12	1.18
16. PREP. - OTHER	19	31	29	69	1.06		1.44	0.82	2.52
17. FINAL INSPECTION	10	40	19	79	0.17		1.08	0.51	2.32
18. METAL HANDLING	1	49	5	93	1.00		0.36	0.07	1.92
19. OTHER RUBBER	7	43	17	81	0.60		0.72	0.29	1.78
20. SALARY	2	48	2	96	0.71		2.00	0.40	10.03
21. UNKNOWN	5	45	14	84	0.77		0.64	0.25	1.66

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 70

ODDS RATIOS FOR COMPANY A SUBJECTS COMPARED WITH THEIR MATCHED CONTROLS
EXPOSURE ≥ 2 YEARS VS. NONE

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	7	41	17	162	1.15		2.0	0.74	5.40
2. MILLING	4	45	21	160	0.92		0.53	0.17	1.63
3. CALENDER	8	39	23	143	0.53		1.26	0.61	2.62
4. TUBER	8	41	17	164	1.31		1.78	0.86	3.65
5. FABRICATION	11	37	21	145	1.74		2.08	1.04	4.15
6. TUBES -FABRICATION	8	40	17	150	1.07		1.67	0.76	3.65
7. CURE PREPARATION	6	44	12	167	0.97		1.78	0.67	4.77
8. CURING	8	38	18	135	0.88		1.46	0.72	2.95
9. INSPECTION	5	45	17	152	0.79		0.61	0.22	1.70
10. MAINTENANCE	7	39	26	138	0.01		1.04	0.51	2.12
11. GENERAL SERVICE	12	27	45	86	0.52		0.79	0.38	1.66
12. SHIP. & REC.	4	46	13	167	0.19		1.12	0.43	2.92
13. RECLAIM	3	48	16	164	0.73		0.62	0.21	1.85
14. CHEMICALS	2	48	6	182	0.29		1.30	0.30	5.67
15. PLASTICS	0	52	0	197	---		---	---	---
16. PREP. - OTHER	2	46	2	175	1.24		3.1	0.69	13.99
17. FINAL INSPECTION	0	47	5	169	1.15		0.00	---	---
18. METAL HANDLING	16	25	43	92	1.28		1.59	0.87	2.90
19. OTHER RUBBER	0	51	2	191	0.71		0.00	---	---
20. SALARY	2	50	10	181	0.33		0.76	0.19	3.05
21. UNKNOWN	4	43	17	152	0.33		0.82	0.32	2.14

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 71

ODDS RATIOS FOR COMPANY A SUBJECTS COMPARED WITH THEIR MATCHED CONTROLS
EXPOSURE >5 YEARS VS. NONE

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	7	41	16	162	1.17		2.03	0.75	5.47
2. MILLING	2	45	15	155	1.26		0.29	0.06	1.46
3. CALENDER	8	39	19	143	1.00		1.58	0.74	3.38
4. TUBER	7	41	9	157	1.62		2.26	0.99	5.15
5. FABRICATION	10	37	17	142	1.84		2.27	1.09	4.73
6. TUBES -FABRICATION	5	40	8	141	1.27		2.16	0.80	5.88
7. CURE PREPARATION	1	44	3	155	0.02		1.02	0.16	6.64
8. CURING	7	38	11	132	1.41		1.94	0.89	4.23
9. INSPECTION	3	45	9	152	0.19		1.13	0.38	3.34
10. MAINTENANCE	3	37	20	124	1.04		0.53	0.20	1.44
11. GENERAL SERVICE	10	27	33	81	0.11		0.94	0.39	2.26
12. SHIP. & REC.	4	46	10	164	0.04		1.03	0.35	3.03
13. RECLAIM	2	48	14	161	1.02		0.47	0.14	1.60
14. CHEMICALS	1	48	6	178	0.53		0.50	0.06	4.30
15. PLASTICS	0	52	0	197	---		---	---	---
16. PREP. - OTHER	2	46	1	175	1.77		6.2	1.15	33.57
17. FINAL INSPECTION	0	47	3	169	0.91		0.00	---	---
18. METAL HANDLING	9	25	28	73	0.09		0.96	0.45	2.06
19. OTHER RUBBER	0	51	0	191	---		---	---	---
20. SALARY	1	50	5	178	0.20		0.80	0.13	4.84
21. UNKNOWN	3	43	8	149	0.27		1.21	0.39	3.79

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 72

ODDS RATIOS FOR COMPANY A SUBJECTS COMPARED WITH THEIR MATCHED CONTROLS
EXPOSURE ≥ 10 YEARS VS. NONE

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	4	41	10	149	0.67		1.61	0.50	5.22
2. MILLING	1	45	12	152	1.70		0.00	---	---
3. CALENDER	5	39	15	134	0.14		1.08	0.43	2.70
4. TUBER	3	41	6	146	0.78		1.70	0.55	5.23
5. FABRICATION	7	37	13	134	1.31		1.91	0.85	4.31
6. TUBES-FABRICATION	5	40	5	135	1.07		2.43	0.62	9.52
7. CURE PREPARATION	1	44	1	155	0.93		3.75	0.36	38.56
8. CURING	5	38	9	125	0.86		1.60	0.65	3.96
9. INSPECTION	2	45	8	148	0.26		0.81	0.22	2.97
10. MAINTENANCE	2	39	12	121	0.77		0.57	0.17	1.91
11. GENERAL SERVICE	5	27	15	75	0.10		0.94	0.32	2.79
12. SHIP. & REC.	2	46	6	161	0.14		1.12	0.30	4.20
13. RECLAIM	2	48	9	161	0.45		0.70	0.19	2.61
14. CHEMICALS	1	48	5	178	0.38		0.59	0.06	5.79
15. PLASTICS	0	52	0	197	---		---	---	---
16. PREP. - OTHER	0	46	0	168	---		---	---	---
17. FINAL INSPECTION	0	47	2	169	0.71		0.00	---	---
18. METAL HANDLING	4	24	15	63	0.51		0.73	0.26	2.02
19. OTHER RUBBER	0	51	0	191	---		---	---	---
20. SALARY	0	50	2	174	0.71		0.00	---	---
21. UNKNOWN	1	43	3	144	0.08		1.09	0.18	6.54

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 73

ODDS RATIOS FOR COMPANY B CASES COMPARED WITH THEIR MATCHED CONTROLS
EXPOSURE ≥ 2 YEARS VS. NONE

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	11	34	28	131	0.89		1.46	0.73	2.91
2. MILLING	1	50	16	175	1.57		0.24	0.05	1.07
3. CALENDER	5	38	38	104	2.38	*	0.26	0.10	0.66
4. TUBER	2	44	14	147	0.98		0.47	0.13	1.67
5. FABRICATION	12	29	28	102	1.17		1.66	0.81	3.39
6. TUBES-FABRICATION	7	37	35	116	1.08		0.63	0.31	1.27
7. CURE PREPARATION	3	41	13	142	0.26		0.84	0.28	2.56
8. CURING	8	34	33	111	0.53		0.79	0.33	1.63
9. INSPECTION	10	35	20	126	1.15		1.75	0.78	3.93
10. MAINTENANCE	10	35	38	130	0.22		0.90	0.40	2.02
11. GENERAL SERVICE	12	32	52	89	1.43		0.54	0.26	1.10
12. SHIP. & REC.	5	40	13	144	0.74		1.57	0.58	4.28
13. RECLAIM	1	44	8	159	0.72		0.48	0.09	2.52
14. CHEMICALS	0	50	5	183	1.15		0.00	---	---
15. PLASTICS	3	45	14	156	0.43		0.73	0.21	2.49
16. PREP. - OTHER	11	31	25	113	1.29		1.71	0.86	3.39
17. FINAL INSPECTION	5	40	15	139	0.20		1.12	0.45	2.76
18. METAL HANDLING	1	49	7	182	0.83		0.48	0.11	2.07
19. OTHER RUBBER	4	43	23	146	0.90		0.60	0.24	1.52
20. SALARY	1	48	2	190	0.58		2.00	0.28	14.43
21. UNKNOWN	1	45	10	158	1.03		0.36	0.07	1.85

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 74

ODDS RATIOS FOR COMPANY B SUBJECTS COMPARED WITH THEIR MATCHED CONTROLS
EXPOSURE ≥ 5 YEARS VS. NONE

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	10	34	22	129	1.18		1.66	0.82	3.35
2. MILLING	1	49	6	175	0.46		0.62	0.11	3.49
3. CALENDER	3	38	22	99	2.17	*	0.19	0.05	0.67
4. TUBER	2	44	5	147	0.34		1.32	0.34	5.13
5. FABRICATION	11	29	21	100	1.49		1.97	0.93	4.14
6. TUBES - FABRICATION	3	37	23	108	1.67		0.39	0.16	0.99
7. CURE PREPARATION	2	41	5	139	0.36		1.36	0.33	5.61
8. CURING	6	34	22	107	0.39		0.83	0.39	1.80
9. INSPECTION	6	35	12	117	0.47		1.30	0.52	3.24
10. MAINTENANCE	10	35	37	130	0.14		0.93	0.42	2.06
11. GENERAL SERVICE	11	32	35	86	0.74		0.71	0.33	1.53
12. SHIP. & REC.	4	40	11	142	0.56		1.44	0.49	4.17
13. RECLAIM	1	44	3	159	0.18		1.23	0.19	7.89
14. CHEMICALS	0	50	1	183	0.58		0.00	---	---
15. PLASTICS	2	45	12	152	0.88		0.43	0.09	2.03
16. PREP. - OTHER	8	31	13	104	1.61		2.33	0.98	5.52
17. FINAL INSPECTION	4	40	7	138	1.06		1.95	0.69	5.50
18. METAL HANDLING	1	49	5	182	0.53		0.63	0.15	2.64
19. OTHER RUBBER	1	43	5	135	0.46		0.58	0.08	4.07
20. SALARY	1	48	0	190	2.00	*	---	---	---
21. UNKNOWN	0	45	4	155	1.11		0.00	---	---

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 75

ODDS RATIOS FOR COMPANY B CASES COMPARED WITH THEIR MATCHED CONTROLS
EXPOSURE ≥ 10 YEARS VS. NONE

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	6	34	16	118	0.48		1.30	0.54	3.12
2. MILLING	1	49	4	175	0.11		0.89	0.15	5.34
3. CALENDER	3	38	19	99	1.95		0.22	0.06	0.79
4. TUBER	1	44	0	144	1.73		---	---	---
5. FABRICATION	9	29	15	97	1.61		2.16	0.98	4.74
6. TUBES-FABRICATION	1	37	14	100	1.94		0.17	0.04	0.76
7. CURE PREPARATION	1	41	2	136	0.41		1.67	0.21	12.95
8. CURING	2	34	140	95	1.70		0.25	0.07	0.95
9. INSPECTION	4	35	8	115	0.46		1.33	0.47	3.73
10. MAINTENANCE	9	35	33	130	0.12		1.06	0.48	2.32
11. GENERAL SERVICE	7	32	22	83	0.34		0.84	0.36	1.97
12. SHIP. & REC.	3	40	8	139	0.49		1.42	0.44	4.59
13. RECLAIM	1	44	2	159	0.49		1.78	0.26	12.23
14. CHEMICALS	0	50	1	183	0.58		0.00	---	---
15. PLASTICS	0	45	2	148	0.86		0.00	---	---
16. PREP. - OTHER	5	31	8	97	1.21		2.21	0.75	6.50
17. FINAL INSPECTION	3	40	3	134	1.51		3.41	0.90	12.99
18. METAL HANDLING	1	49	3	182	0.12		0.89	0.19	4.23
19. OTHER RUBBER	0	43	1	133	0.50		0.00	---	---
20. SALARY	0	44	0	186	---		---	---	---
21. UNKNOWN	0	45	1	155	0.50		0.00	---	---

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 76

ODDS RATIOS FOR ALL CONFIRMED CASES, COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER.

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	17	47	54	195	0.89		1.41	0.75	2.65
2. MILLING	5		31	218	1.17		0.53	0.21	1.30
3. CALENDER	16		69	180	0.50		0.85	0.49	1.46
4. TUBER	10		34	215	0.46		1.19	0.64	2.19
5. FABRICATION	22		72	177	0.83		1.31	0.77	2.22
6. TUBES-FABRICATION	15		69	180	0.72		0.78	0.44	1.38
7. CURE PREPARATION	9		31	218	0.41		1.18	0.61	2.27
8. CURING	15		71	178	0.86		0.76	0.44	1.29
9. INSPECTION	12		73	176	1.10		0.65	0.34	1.24
10. MAINTENANCE	18		55	194	1.08		1.44	0.82	2.51
11. GENERAL SERVICE	27		115	134	0.58		0.84	0.51	1.38
12. SHIP. & REC.	11		35	214	0.64		1.29	0.67	2.48
13. RECLAIM	5		28	221	0.81		0.67	0.29	1.52
14. CHEMICALS	3		11	238	0.07		1.05	0.33	3.36
15. PLASTICS	2		18	231	1.22		0.36	0.09	1.43
16. PREP. - OTHER	12		44	205	0.16		1.06	0.60	1.86
17. FINAL INSPECTION	8		35	214	0.35		0.86	0.41	1.77
18. METAL HANDLING	21		61	188	1.50		1.72	0.95	3.12
19. OTHER RUBBER	4		32	217	1.50		0.44	0.18	1.08
20. SALARY	4		11	238	0.68		1.50	0.56	4.00
21. UNKNOWN	9		35	214	0.02		1.01	0.46	2.20

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 77

ODDS RATIOS FOR ALL UNCONFIRMED CASES, COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	10	28	27	127	1.21		1.59	0.85	2.99
2. MILLING	3	35	18	136	0.91		0.50	0.14	1.73
3. CALENDER	8	30	45	109	0.95		0.69	0.37	1.31
4. TUBER	7	31	25	129	0.06		1.03	0.49	2.14
5. FABRICATION	14	24	47	107	0.55		1.26	0.63	2.54
6. TUBES-FABRICATION	10	28	34	120	0.42		1.17	0.63	2.19
7. CURE PREPARATION	8	30	18	136	1.44		1.88	0.92	3.83
8. CURING	15	23	32	122	2.26		2.29	1.26	4.19
9. INSPECTION	10	28	27	127	1.20		1.84	0.79	4.25
10. MAINTENANCE	10	28	38	116	0.07		1.03	0.49	2.15
11. GENERAL SERVICE	16	22	52	102	0.49		1.19	0.67	2.10
12. SHIP. & REC.	5	33	23	131	0.38		0.83	0.37	1.85
13. RECLAIM	5	33	20	134	0.10		0.95	0.41	2.21
14. CHEMICALS	1	37	9	145	0.83		0.44	0.09	2.21
15. PLASTICS	3	35	18	136	0.83		0.54	0.16	1.83
16. PREP. - OTHER	12	26	25	129	2.05		2.49	1.20	5.17
17. FINAL INSPECTION	7	31	21	133	0.66		1.40	0.60	3.27
18. METAL HANDLING	7	31	34	120	1.17		0.53	0.22	1.29
19. OTHER RUBBER	4	34	15	139	0.10		1.08	0.30	3.84
20. SALARY	0	38	7	147	1.32		0.00	---	---
21. UNKNOWN	6	32	26	128	0.24		0.88	0.38	2.06

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 78

ODDS RATIOS FOR ALL CASES WHO ENTERED THE INDUSTRY AT AGE ≤ 24 ,
 COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	12	28	40	115	0.58		1.28	0.64	2.57
2. MILLING	3	37	22	133	1.10		0.49	0.17	1.43
3. CALENDER	15	25	46	109	0.71		1.29	0.72	2.32
4. TUBER	9	31	28	127	0.65		1.29	0.68	2.47
5. FABRICATION	24	16	60	95	2.41	*	2.47	1.33	4.57
6. TUBES -FABRICATION	10	30	42	113	0.24		0.89	0.41	1.95
7. CURE PREPARATION	12	28	18	137	2.90	*	2.93	1.59	5.40
8. CURING	18	22	47	108	1.82		1.80	1.06	3.06
9. INSPECTION	14	26	44	111	0.82		1.48	0.68	3.25
10. MAINTENANCE	14	26	38	117	1.37		1.72	0.90	3.29
11. GENERAL SERVICE	17	23	70	85	0.31		0.90	0.51	1.60
12. SHIP. & REC.	7	33	27	128	0.02		0.99	0.45	2.18
13. RECLAIM	5	35	16	139	0.44		1.25	0.55	2.84
14. CHEMICALS	3	37	9	146	0.38		1.31	0.40	4.30
15. PLASTICS	0	40	14	141	2.11	*	0.00	---	---
16. PREP. - OTHER	13	27	30	125	1.90		2.16	1.11	4.22
17. FINAL INSPECTION	6	34	23	132	0.03		0.99	0.40	2.41
18. METAL HANDLING	8	32	38	117	0.67		0.70	0.30	1.67
19. OTHER RUBBER	3	37	19	136	0.90		0.51	0.15	1.75
20. SALARY	2	38	9	146	0.16		0.88	0.23	3.40
21. UNKNOWN	7	33	25	130	0.21		1.10	0.51	2.38

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 79

ODDS RATIOS FOR ALL CASES WHO ENTERED THE INDUSTRY AT AGE >24
COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	15	47	41	197	1.40		1.67	0.92	3.03
2. MILLING	5	57	27	211	0.99		0.54	0.20	1.49
3. CALENDER	10	52	65	173	1.83		0.50	0.28	0.92
4. TUBER	8	54	31	207	0.09		0.96	0.48	1.92
5. FABRICATION	12	50	59	179	0.89		0.72	0.39	1.33
6. TUBES - FABRICATION	15	47	61	177	0.24		0.93	0.57	1.53
7. CURE PREPARATION	5	57	31	207	1.02		0.58	0.25	1.39
8. CURING	12	50	57	181	0.67		0.79	0.44	1.42
9. INSPECTION	8	54	46	192	1.12		0.63	0.32	1.24
10. MAINTENANCE	14	48	55	183	0.00		1.00	---	---
11. GENERAL SERVICE	26	36	98	140	0.02		1.01	0.62	1.65
12. SHIP. & REC.	9	43	31	207	0.38		1.17	0.59	2.32
13. RECLAIM	5	57	32	206	1.15		0.56	0.24	1.28
14. CHEMICALS	1	61	11	227	1.06		0.36	0.08	1.76
15. PLASTICS	5	57	22	216	0.25		0.85	0.30	2.44
16. PREP. - OTHER	11	51	39	199	0.27		1.10	0.60	2.01
17. FINAL INSPECTION	9	53	33	205	0.16		1.07	0.53	2.18
18. METAL HANDLING	20	42	61	177	1.13		1.50	0.83	2.71
19. OTHER RUBBER	5	57	28	210	0.79		0.65	0.27	1.59
20. SALARY	2	60	9	229	0.15		0.89	0.25	3.20
21. UNKNOWN	8	54	36	202	0.39		0.83	0.37	1.86

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 80

ODDS RATIOS FOR COMPANY A SUBJECTS WHO ENTERED THE INDUSTRY AT AGE ≤ 24 ,
 COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	4	14	11	59	0.81		1.83	0.54	6.27
2. MILLING	2	16	10	60	0.31		0.75	0.16	3.47
3. CALENDER	8	10	11	59	2.77		4.76	1.89	12.01
4. TUBER	6	12	10	60	1.86		2.49	1.11	5.57
5. FABRICATION	9	9	23	47	1.28		1.91	0.83	4.36
6. TUBES - FABRICATION	4	14	14	56	0.26		1.19	0.39	3.62
7. CURE PREPARATION	4	14	6	64	1.77		3.00	1.08	8.34
8. CURING	8	10	17	53	1.73		2.34	1.04	5.26
9. INSPECTION	2	16	14	56	0.91		0.38	0.07	2.19
10. MAINTENANCE	6	12	20	50	0.43		1.28	0.49	3.34
11. GENERAL SERVICE	10	8	26	44	1.40		2.00	0.89	4.50
12. SHIP. & REC.	3	15	9	61	0.44		1.44	0.37	5.59
13. RECLAIM	1	17	8	62	0.76		0.50	0.11	2.26
14. CHEMICALS	3	15	3	67	1.89		5.25	1.24	22.25
15. PLASTICS	0	18	0	70	---		---	---	---
16. PREP. - OTHER	2	16	0	70	1.19		2.13	0.75	6.06
17. FINAL INSPECTION	2	16	4	66	0.74		2.17	0.39	12.04
18. METAL HANDLING	8	8	33	37	0.21		0.89	0.36	2.18
19. OTHER RUBBER	1	17	1	69	0.93		3.75	0.36	38.56
20. SALARY	1	17	9	61	0.86		0.38	0.06	2.46
21. UNKNOWN	4	14	10	60	0.81		1.64	0.60	4.48

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 81

ODDS RATIOS FOR COMPANY A SUBJECTS WHO ENTERED THE INDUSTRY AT AGE >24,
 COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	7	27	17	110	1.22		1.96	0.79	4.83
2. MILLING	5	29	18	109	0.10		0.93	0.31	2.82
3. CALENDER	5	29	26	101	0.73		0.69	0.29	1.60
4. TUBER	5	29	14	113	0.47		1.31	0.51	3.41
5. FABRICATION	6	28	19	108	0.32		1.20	0.47	3.02
6. TUBES -FABRICATION	8	26	22	105	0.80		1.46	0.68	3.13
7. CURE PREPARATION	4	30	12	115	0.51		1.42	0.46	4.39
8. CURING	6	28	27	100	0.40		0.81	0.34	1.94
9. INSPECTION	5	29	19	108	0.08		1.04	0.45	2.43
10. MAINTENANCE	7	27	23	104	0.43		1.22	0.57	2.64
11. GENERAL SERVICE	15	19	50	77	0.43		1.20	0.59	2.43
12. SHIP. & REC.	3	31	15	112	0.44		0.75	0.26	2.17
13. RECLAIM	3	31	21	106	1.10		0.50	0.18	1.41
14. CHEMICALS	1	33	4	123	0.00		1.00	---	---
15. PLASTICS	0	34	0	127	---		---	---	---
16. PREP. - OTHER	3	31	7	120	0.61		1.54	0.49	4.84
17. FINAL INSPECTION	3	31	8	119	0.45		1.37	0.43	4.36
18. METAL HANDLING	19	15	52	75	1.71		2.01	1.03	3.93
19. OTHER RUBBER	0	34	2	125	0.71		0.00	---	---
20. SALARY	1	33	7	120	0.53		0.57	0.10	3.25
21. UNKNOWN	6	28	23	104	0.06		1.04	0.37	2.93

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 82

ODDS RATIOS FOR COMPANY B SUBJECTS WHO ENTERED THE INDUSTRY AT AGE ≤ 24 ,
 COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	8	14	29	56	0.20		1.10	0.48	2.57
2. MILLING	1	21	12	73	1.21		0.32	0.07	1.51
3. CALENDER	7	15	38	47	1.16		0.54	0.22	1.29
4. TUBER	3	19	18	67	0.79		0.58	0.19	1.81
5. FABRICATION	15	7	37	48	2.08	*	3.23	1.28	8.17
6. TUBES -FABRICATION	6	16	28	58	0.48		0.73	0.24	2.16
7. CURE PREPARATION	8	14	12	73	2.31	*	2.90	1.36	6.20
8. CURING	10	12	30	55	0.92		1.49	0.73	3.02
9. INSPECTION	12	10	27	58	1.69		2.61	1.03	6.64
10. MAINTENANCE	8	14	18	67	1.53		2.30	0.94	5.63
11. GENERAL SERVICE	7	15	44	41	1.70		0.39	0.16	0.97
12. SHIP. & REC.	4	18	18	67	0.34		0.82	0.33	2.07
13. RECLAIM	4	18	8	77	1.16		2.07	0.74	5.81
14. CHEMICALS	0	22	6	79	1.22		0.00	---	---
15. PLASTICS	0	22	14	71	2.11	*	0.00	---	---
16. PREP. - OTHER	11	11	27	58	1.58		2.17	0.97	4.85
17. FINAL INSPECTION	4	18	19	66	0.44		0.75	0.26	2.17
18. METAL HANDLING	0	22	5	80	1.18		0.00	---	---
19. OTHER RUBBER	2	20	18	67	1.32		0.28	0.06	1.37
20. SALARY	1	21	0	85	2.00	*	---	---	---
21. UNKNOWN	3	19	15	70	0.45		0.72	0.22	2.29

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 83

ODDS RATIOS FOR COMPANY B SUBJECTS WHO ENTERED THE INDUSTRY AT AGE >24,
COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	8	20	24	87	0.79		1.47	0.66	3.28
2. MILLING	0	28	9	102	1.59		0.00	---	---
3. CALENDER	5	23	39	72	1.95		0.36	0.15	0.85
4. TUBER	3	25	17	94	0.61		0.69	0.25	1.90
5. FABRICATION	6	22	40	71	1.42		0.48	0.20	1.12
6. TUBES-FABRICATION	7	21	31	80	1.10		0.64	0.32	1.25
7. CURE PREPARATION	1	27	19	92	1.85		0.17	0.03	0.82
8. CURING	6	22	29	82	0.55		0.77	0.34	1.70
9. INSPECTION	3	25	27	84	1.66		0.32	0.10	0.99
10. MAINTENANCE	7	21	32	79	0.42		0.78	0.29	2.03
11. GENERAL SERVICE	11	17	48	63	0.44		0.83	0.41	1.67
12. SHIP. & REC.	6	22	16	95	0.92		1.67	0.67	4.17
13. RECLAIM	2	26	11	100	0.46		0.68	0.17	2.70
14. CHEMICALS	0	28	7	104	1.37		0.00	---	---
15. PLASTICS	5	23	22	89	0.25		0.85	0.30	2.44
16. PREP. - OTHER	8	20	32	79	0.05		0.98	0.48	2.02
17. FINAL INSPECTION	6	22	21	90	0.14		0.93	0.38	2.28
18. METAL HANDLING	1	27	9	101	1.01		0.41	0.10	1.76
19. OTHER RUBBER	5	23	26	85	0.62		0.71	0.29	1.75
20. SALARY	1	27	2	109	0.58		2.00	0.28	14.43
21. UNKNOWN	2	26	13	98	0.67		0.58	0.15	2.20

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 84

ODDS RATIOS FOR COMPANY A SUBJECTS WHO DIED AT AGE <65,
 COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG	CASES		CONTROLS		CMI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	3	9	7	39	1.02		2.25	0.61	8.31
2. MILLING	2	10	8	38	0.00		1.00	---	---
3. CALENDER	6	6	11	35	1.80		3.24	1.11	9.49
4. TUBER	3	9	10	36	0.27		1.19	0.41	3.44
5. FABRICATION	5	7	18	28	0.13		1.09	0.36	3.26
6. TUBES-FABRICATION	4	8	12	34	0.60		1.52	0.49	4.73
7. CURE PREPARATION	3	9	6	40	1.10		2.00	0.71	5.67
8. CURING	6	6	10	36	2.01		3.29	1.24	8.72
9. INSPECTION	1	11	10	36	1.06		0.24	0.02	2.21
10. MAINTENANCE	5	7	13	33	0.58		1.62	0.57	4.60
11. GENERAL SERVICE	9	3	14	32	2.55		5.76	1.86	17.82
12. SHIP. & REC.	3	9	5	41	1.07		2.35	0.63	8.73
13. RECLAIM	1	11	7	39	0.61		0.57	0.13	2.57
14. CHEMICALS	3	9	3	43	1.89		5.25	1.24	22.25
15. PLASTICS	0	12	0	46	---		---	---	---
16. PREP. - OTHER	2	10	1	45	0.80		1.68	0.57	4.94
17. FINAL INSPECTION	2	10	1	45	2.03		---	---	---
18. METAL HANDLING	7	5	25	21	0.27		1.19	0.41	3.42
19. OTHER RUBBER	1	11	0	46	1.73		---	---	---
20. SALARY	1	11	9	37	0.86		0.38	0.06	2.46
21. UNKNOWN	2	10	5	41	0.53		1.55	0.40	6.01

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 85

ODDS RATIOS FOR COMPANY A SUBJECTS WHO DIED AT AGE >65,
COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	8	32	21	130	1.12		1.81	0.76	4.32
2. MILLING	5	35	20	131	0.33		0.80	0.28	2.34
3. CALENDER	7	33	26	125	0.03		1.01	0.48	2.12
4. TUBER	8	32	14	137	1.76		2.27	1.06	4.89
5. FABRICATION	10	30	24	127	1.29		1.80	0.85	3.79
6. TUBES -FABRICATION	8	32	24	127	0.58		1.31	0.61	2.79
7. CURE PREPARATION	5	35	12	139	1.03		1.97	0.67	5.82
8. CURING	8	32	34	117	0.27		0.83	0.42	1.88
9. INSPECTION	6	34	23	128	0.08		1.04	0.45	2.38
10. MAINTENANCE	8	32	29	122	0.21		1.10	0.52	2.39
11. GENERAL SERVICE	16	24	61	90	0.12		0.95	0.50	1.80
12. SHIP. & REC.	3	37	18	133	0.76		0.60	0.20	1.82
13. RECLAIM	3	37	22	129	1.18		0.48	0.17	1.34
14. CHEMICALS	1	39	4	147	0.00		1.00	---	---
15. PLASTICS	0	40	0	151	---		---	---	---
16. PREP. - OTHER	3	37	6	145	0.82		1.78	0.56	5.71
17. FINAL INSPECTION	3	37	11	140	0.01		1.01	0.35	2.86
18. METAL HANDLING	20	20	60	91	1.25		1.59	0.86	2.94
19. OTHER RUBBER	0	40	3	148	0.87		0.00	---	---
20. SALARY	1	39	7	144	0.53		0.57	0.10	3.25
21. UNKNOWN	8	32	28	123	0.34		1.19	0.51	2.79

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 86

ODDS RATIOS FOR COMPANY B CASES WHO DIED AT AGE ≤ 65 ,
 COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTC	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	3	8	10	32	0.20		1.15	0.35	3.80
2. MILLING	1	10	4	38	0.00		1.00	---	---
3. CALENDER	1	10	16	26	2.10		0.00	---	---
4. TUBER	1	10	8	34	0.78		0.43	0.07	2.53
5. FABRICATION	2	9	10	32	1.03		0.36	0.07	1.84
6. TUBES -FABRICATION	2	9	12	30	1.08		0.38	0.09	1.66
7. CURE PREPARATION	0	11	2	40	0.82		0.00	---	---
8. CURING	5	6	13	29	0.81		1.71	0.58	5.03
9. INSPECTION	2	9	6	36	0.30		1.43	0.20	10.25
10. MAINTENANCE	3	8	14	28	0.36		0.69	0.13	3.73
11. GENERAL SERVICE	4	7	18	24	0.48		0.71	0.22	2.31
12. SHIP. & REC.	2	9	6	36	0.35		1.41	0.28	7.03
13. RECLAIM	2	9	3	39	1.10		3.11	0.57	17.01
14. CHEMICALS	0	11	5	37	1.18		0.00	---	---
15. PLASTICS	2	9	13	29	0.82		0.48	0.11	2.10
16. PREP. - OTHER	5	6	17	25	0.26		1.17	0.43	3.23
17. FINAL INSPECTION	4	7	12	30	0.47		1.45	0.40	5.23
18. METAL HANDLING	0	11	7	35	1.70		0.00	---	---
19. OTHER RUBBER	2	9	14	28	0.00		1.00	---	---
20. SALARY	0	11	0	42	---		---	---	---
21. UNKNOWN	1	10	4	38	0.00		1.00	---	---

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 87

ODDS RATIOS FOR COMPANY B CASES WHO DIED AT AGE >65,
COMPARED WITH THEIR MATCHED CONTROLS. EXPOSURE = EVER-NEVER

OTG	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
1. BATCH PREPARATION	13	26	43	111	0.66		1.31	0.67	2.55
2. MILLING	0	39	17	137	2.20		0.00	---	---
3. CALENDER	11	28	61	93	1.44		0.57	0.30	1.08
4. TUBER	5	34	27	127	0.71		0.69	0.30	1.61
5. FABRICATION	19	20	63	91	0.87		1.40	0.74	2.67
6. TUBES -FABRICATION	11	28	53	101	0.75		0.75	0.39	1.41
7. CURE PREPARATION	9	30	29	125	0.57		1.25	0.66	2.37
8. CURING	11	28	46	108	0.19		0.93	0.51	1.71
9. INSPECTION	13	26	51	103	0.02		0.99	0.47	2.08
10. MAINTENANCE	12	27	36	118	0.94		1.50	0.74	3.04
11. GENERAL SERVICE	14	25	74	80	1.41		0.59	0.31	1.09
12. SHIP. & REC.	8	31	28	126	0.29		1.13	0.56	2.28
13. RECLAIM	4	35	16	138	0.03		0.98	0.39	2.46
14. CHEMICALS	0	39	8	146	1.41		0.00	---	---
15. PLASTICS	3	36	23	131	1.22		0.42	0.13	1.36
16. PREP. - OTHER	14	25	42	112	1.04		1.48	0.80	2.73
17. FINAL INSPECTION	6	33	32	122	0.79		0.67	0.30	1.53
18. METAL HANDLING	1	38	7	147	0.55		0.57	0.11	3.07
19. OTHER RUBBER	5	34	36	118	1.41		0.50	0.22	1.12
20. SALARY	2	37	2	152	1.50		4.00	0.87	18.29
21. UNKNOWN	4	35	24	130	0.86		0.60	0.23	1.59

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 88

ODDS RATIOS FOR COMPANY A SUBJECTS WITH POTENTIAL EXPOSURE TO
POLYCYCLIC HYDROCARBONS, COMPARED WITH THEIR MATCHED CONTROLS

	<u>CASES</u>		<u>CONTROLS</u>		<u>CHI</u>	<u>P-VALUE</u>	<u>OR</u>	<u>CONFIDENCE INTERVAL</u>	
	<u>EXP</u>	<u>UNEXP</u>	<u>EXP</u>	<u>UNEXP</u>				<u>LOW</u>	<u>HIGH</u>
EXPOSURE = EVER-NEVER									
1. High Exposure ^(a)	17	35	54	143	0.87		1.34	0.77	2.35
2. High or Mod. Exp.	27	25	97	100	0.34		1.10	0.68	1.79
EXPOSURE ≥2 yrs. vs. N.									
1. High Exposure	12	34	34	121	0.58		1.25	0.66	2.36
2. High or Mod. Exp.	20	23	63	78	0.21		1.08	0.61	1.91
EXPOSURE ≥5 yrs. vs. N.									
1. High Exposure	8	34	23	109	0.05		0.98	0.46	2.09
2. High or Mod. Exp.	17	23	48	71	0.14		1.05	0.56	1.97
EXPOSURE ≥10 yrs. vs. N.									
1. High Exposure	6	33	14	107	0.60		1.37	0.58	3.25
2. High or Mod. Exp.	11	23	30	68	0.44		1.19	0.62	2.31

* = probability ≤ 0.05 ** = probability ≤ 0.01

(a) See Appendix III and Table 98

TABLE 89

ODDS RATIOS FOR COMPANY B SUBJECTS WITH POTENTIAL EXPOSURE TO
POLYCYCLIC HYDROCARBONS, COMPARED WITH THEIR MATCHED CONTROLS

	<u>CASES</u>		<u>CONTROLS</u>		<u>CHI</u>	<u>P-VALUE</u>	<u>OR</u>	<u>CONFIDENCE INTERVAL</u>	
	<u>EXP</u>	<u>UNEXP</u>	<u>EXP</u>	<u>UNEXP</u>				<u>LOW</u>	<u>HIGH</u>
EXPOSURE = EVER-NEVER									
1. High Exposure	22	28	92	104	0.40		0.88	0.52	1.50
2. High or Mod. Exp.	31	19	123	73	0.10		0.96	0.53	1.76
EXPOSURE ≥ 2 yrs. vs. N.									
1. High Exposure	17	27	57	88	0.14		0.95	0.51	1.78
2. High or Mod. Exp.	25	18	81	63	0.18		1.07	0.56	2.04
EXPOSURE ≥ 5 yrs. vs. N.									
1. High Exposure	15	27	38	85	0.69		1.32	0.68	2.58
2. High or Mod. Exp.	24	18	63	62	0.67		1.30	0.68	2.49
EXPOSURE ≥ 10 yrs. vs. N.									
1. High Exposure	10	27	25	75	0.33		1.17	0.53	2.57
2. High or Mod. Exp.	18	18	40	53	0.36		1.17	0.58	2.35

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 90

ODDS RATIOS FOR COMPANY A SUBJECTS WITH POTENTIAL EXPOSURE TO
NITROSAMINES, COMPARED WITH THEIR MATCHED CONTROLS

	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
EXPOSURE = EVER-NEVER									
1. High Exposure (a)	18	34	54	143	0.95		1.37	0.79	2.35
2. High or Mod. Exp.	31	21	104	93	0.91		1.30	0.81	2.10
EXPOSURE ≥ 2 yrs. vs. N.									
1. High Exposure	10	32	36	110	0.15		0.92	0.39	2.17
2. High or Mod. Exp.	27	19	72	78	1.53		1.64	0.96	2.79
EXPOSURE ≥ 5 yrs. vs. N.									
1. High Exposure	6	32	19	102	0.20		0.88	0.31	2.50
2. High or Mod. Exp.	21	19	5	61	1.08		1.49	0.81	2.74
EXPOSURE ≥ 10 yrs. vs. N.									
1. High Exposure	2	32	12	93	1.56		0.14	0.02	1.11
2. High or Mod. Exp.	14	19	34	51	0.40		1.19	0.59	2.42

* = probability ≤ 0.05 ** = probability ≤ 0.01

(a) See Appendix III and Table 98

TABLE 91

ODDS RATIOS FOR COMPANY B CASES WITH POTENTIAL EXPOSURE TO
NITROSAMINES, COMPARED WITH THEIR MATCHED CONTROLS

	<u>CASES</u>		<u>CONTROLS</u>		<u>CHI</u>	<u>P-VALUE</u>	<u>OR</u>	<u>CONFIDENCE INTERVAL</u>	
	<u>EXP</u>	<u>UNEXP</u>	<u>EXP</u>	<u>UNEXP</u>				<u>LOW</u>	<u>HIGH</u>
EXPOSURE = EVER-NEVER									
1. High Exposure	31	19	98	98	1.51		1.63	0.96	2.79
2. High or Mod. Exp.	36	14	131	65	0.70		1.31	0.69	2.46
EXPOSURE ≥ 2 yrs. vs. N.									
1. High Exposure	23	19	60	80	1.46		1.68	0.94	3.02
2. High or Mod. Exp.	30	14	91	57	0.75		1.35	0.70	2.60
EXPOSURE ≥ 5 yrs. vs. N.									
1. High Exposure	21	19	46	76	2.39	*	1.74	0.97	3.12
2. High or Mod. Exp.	28	14	74	55	0.86		1.40	0.74	2.67
EXPOSURE ≥ 10 yrs. vs. N.									
1. High Exposure	13	19	28	61	0.69		1.33	0.67	2.64
2. High or Mod. Exp.	19	14	48	45	0.34		1.16	0.57	2.33

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 92

ODDS RATIOS FOR COMPANY A CASES WITH POTENTIAL EXPOSURE TO
CARBON BLACK, COMPARED WITH THEIR MATCHED CONTROLS

	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
EXPOSURE = EVER-NEVER									
1. High Exposure ^(a)	9	43	21	176	1.66		2.31	1.01	5.29
2. High or Mod. Exp.	21	31	64	133	1.14		1.49	0.84	2.66
EXPOSURE ≥2 yrs. vs. N.									
1. High Exposure	6	42	13	164	1.39		2.52	0.85	7.49
2. High or Mod. Exp.	13	30	38	111	0.60		1.29	0.64	2.61
EXPOSURE ≥5 yrs. vs. N.									
1. High Exposure	6	42	12	164	1.42		2.56	0.86	7.59
2. High or Mod. Exp.	13	30	29	111	1.38		1.87	0.89	3.93
EXPOSURE ≥10 yrs. vs. N.									
1. High Exposure	4	42	7	159	1.36		2.94	0.80	10.87
2. High or Mod. Exp.	7	29	18	97	0.42		1.28	0.48	3.43

* = probability ≤0.05 ** = probability ≤0.01

(a) See Appendix III and Table 98

TABLE 93

ODDS RATIOS FOR COMPANY B SUBJECTS WITH POTENTIAL EXPOSURE TO
CARBON BLACK, COMPARED WITH THEIR MATCHED CONTROLS

	<u>CASES</u>		<u>CONTROLS</u>		<u>CHI</u>	<u>P-VALUE</u>	<u>OR</u>	<u>CONFIDENCE INTERVAL</u>	
	<u>EXP</u>	<u>UNEXP</u>	<u>EXP</u>	<u>UNEXP</u>				<u>LOW</u>	<u>HIGH</u>
EXPOSURE = EVER-NEVER									
1. High Exposure	14	36	41	155	1.06		1.45	0.81	2.59
2. High or Mod. Exp.	33	17	103	93	1.70		1.74	1.02	2.97
EXPOSURE ≥ 2 yrs. vs. N.									
1. High Exposure	9	36	21	138	1.02		1.58	0.75	3.31
2. High or Mod. Exp.	24	17	60	69	1.23		1.58	0.86	2.90
EXPOSURE ≥ 5 yrs. vs. N.									
1. High Exposure	8	36	16	135	1.23		1.79	0.82	3.88
2. High or Mod. Exp.	22	17	46	63	1.26		1.66	0.86	3.23
EXPOSURE ≥ 10 yrs. vs. N.									
1. High Exposure	5	36	10	126	0.99		1.76	0.69	4.50
2. High or Mod. Exp.	14	17	30	52	0.90		1.56	0.69	2.51

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 94

ODDS RATIOS FOR COMPANY A CASES WITH POTENTIAL EXPOSURE TO
ASBESTOS, COMPARED WITH THEIR MATCHED CONTROLS

	CASES		CONTROLS		CHI	P-VALUE	OR	CONFIDENCE INTERVAL	
	EXP	UNEXP	EXP	UNEXP				LOW	HIGH
EXPOSURE = EVER-NEVER									
1. High Exposure ^(a)	13	39	40	157	0.72		1.32	0.70	2.50
2. High or Mod. Exp.	27	25	64	133	2.69	**	2.41	1.41	4.13
EXPOSURE ≥2 yrs. vs. N.									
1. High Exposure	9	39	19	145	1.14		1.70	0.79	3.68
2. High or Mod. Exp.	16	25	28	108	2.26	*	2.48	1.28	4.81
EXPOSURE ≥5 yrs. vs. N.									
1. High Exposure	7	39	9	140	1.86		2.70	1.12	6.50
2. High or Mod. Exp.	13	25	18	101	2.37	*	2.75	1.36	5.56
EXPOSURE ≥10 yrs. vs. N.									
1. High Exposure	3	39	4	129	1.33		3.18	0.76	13.25
2. High or Mod. Exp.	7	25	9	87	1.85		2.72	1.12	6.65

* = probability ≤0.05 ** = probability ≤0.01

(a) See Appendix III and Table 98

TABLE 95

ODDS RATIOS FOR COMPANY B SUBJECTS WITH POTENTIAL EXPOSURE TO
ASBESTOS, COMPARED WITH THEIR MATCHED CONTROLS

	<u>CASES</u>		<u>CONTROLS</u>		<u>CHI</u>	<u>P-VALUE</u>	<u>OR</u>	<u>CONFIDENCE INTERVAL</u>	
	<u>EXP</u>	<u>UNEXP</u>	<u>EXP</u>	<u>UNEXP</u>				<u>LOW</u>	<u>HIGH</u>
EXPOSURE = EVER-NEVER									
1. High Exposure	12	38	78	118	2.14	*	0.46	0.26	0.84
2. High or Mod. Exp.	33	17	122	74	0.46		1.16	0.68	2.00
EXPOSURE ≥ 2 yrs. vs. N.									
1. High Exposure	9	37	46	105	1.46		0.56	0.29	1.08
2. High or Mod. Exp.	26	16	76	58	0.64		1.27	0.68	2.35
EXPOSURE ≥ 5 yrs. vs. N.									
1. High Exposure	4	37	32	94	2.20	*	0.29	0.11	0.73
2. High or Mod. Exp.	21	16	49	51	0.82		1.38	0.72	2.64
EXPOSURE ≥ 10 yrs. vs. N.									
1. High Exposure	2	37	20	89	2.20	*	0.20	0.06	0.66
2. High or Mod. Exp.	14	16	30	43	0.52		1.26	0.60	2.64

* = probability ≤ 0.05 ** = probability ≤ 0.01

TABLE 96

UNMATCHED ODDS RATIOS FOR POTENTIAL ASBESTOS EXPOSURE,
BY DECADE OF ENTRY INTO THE INDUSTRY

<u>DECADE</u>	<u>CASES</u>		<u>CONTROLS</u>		<u>CHI</u>	<u>OR</u>
	<u>EXP</u>	<u>UNEXP</u>	<u>EXP</u>	<u>UNEXP</u>		
1910-1919	4	7	5	18	0.81	2.05
1920-1929	12	9	25	55	4.80	2.93
1930-1939	0	2	9	13	1.31	-
1940-1949	6	11	19	51	0.44	1.46
1950-1959	1	0	2	2	0.83	-

TABLE 97

UNMATCHED ODDS RATIOS FOR POTENTIAL ASBESTOS EXPOSURE AT VARYING LATENCY¹ PERIODS

<u>CASES</u>			<u>CONTROLS</u>				
<u>EXP</u>	<u>UNEXP</u>	<u>MEAN EXPOSURE AMONG EXPOSED (IN MONTHS)</u>	<u>EXP</u>	<u>UNEXP</u>	<u>MEAN EXPOSURE AMONG EXPOSED (IN MONTHS)</u>	<u>χ^2</u>	<u>OR</u>
			Latency ≥ 40				
13	15	88.1	46	119	60.2	3.88	2.24
			30 $\leq$ Latency < 40				
5	5	81.8	6	6	112.8	-	1
			20 $\leq$ Latency < 30				
5	9	17.8	6	14	61.3	0.14	1.29

¹Latency defined as Year of Death - Year of Hire

TABLE 98

COMPOSITION OF CHEMICAL - SPECIFIC OTGs

I. POTENTIAL ASBESTOS EXPOSURE

1. High Exposure - CMTR, CRTU, FITU, FUSP, MIMG, TUBU
2. Moderate Exposure - BPMC, BPTR, BPTU, INDA, MITU, MNMS, MNCP, SBPU, SBPR, STOX, STTU
3. Low Exposure - CEMG, CRBA, CRFB, CRSX, CRTR, CRVV, MIFB, MIMS, MIPL, MITD, MNMA, MNWR, OTHR, PALI, PIPE, PWPT, RCMi, SREC, TCKR, TEST, TUBC, VVMA
4. No Exposure - All other OTs not included above

II. POTENTIAL CARBON BLACK EXPOSURE

1. High Exposure - BPMC, BPTR, BPTU, PIPE, SBPR, SBPU
2. Moderate Exposure - CMTR, INDA, MNMS, SJAN
3. Low Exposure - CRBA, CRFB, CRSX, CRTR, CRTU, CRVV, FIRA, FIRB, FITU, FUSP, INDC, MIFR, MIMG, MIMS, MIPL, MITD, MITU, MNEC, MNEL, MNWR, RDCV, RCMi, RCPR, REDE, SREC, STOR, TCKR, TEST
4. No Exposure - All others

III. POTENTIAL POLYCYCLIC HYDROCARBONS EXPOSURE

1. High Exposure - BPMC, BPTR, BPTU, CMTR, CRBA, CRFB, CRSX, CRTR, CRTU, CRVV, MIMG, PIPE, RCDV
2. Moderate Exposure - FIRB, INDA, MIFB, MIMS, MIPL, MITD, MITU, RCMi, RCPA, SBPR, SBPU, SREC
3. Low Exposure - BEBL, CALO, CALT, CEMD, CEMG, FIRA, FITU, FUSP, INDC, INRE, MNMS, OTHR, OTNT, PLHA, PWPT, REDE, SJAN, SLIN, SMOL, SRLC, STBB, STOD, STOR, STOX, STTU, TCKR, TEST, TRBL, TUBC, TUBD, TUBU, VVMA
4. No Exposure - All others

IV. POTENTIAL NITROSAMINES EXPOSURE

1. High Exposure - BPMC, BPTR, BPTU, CRSX, FOAM, INDA, MIFB, MIPL, MIMG, MIMS, MIPL, MITD, MITU
2. Moderate Exposure - CALO, CALT, CMTR, CRBA, CRFB, CRTR, CRTU, CRVV, FIRB, RCDV, RCMi, SBPR, SBPU, SMOL, TUBC, TUBD, TUBU
3. Low Exposure - BEBL, CEMD, FIRA, FITU, FUSP, INDC, MNEL, MNWL, SMOL, OTHR, OTNT, PLHA, PLST, RCPR, REDE, ROCK, ROCP, RSMF, SJAN, SLIN, SREC, SRLC, STOD, STOR, STOX, STTU, SYNT, TCKR, TEST, TRBL, URET
4. No Exposure - All others

TABLE 99

SUMMARY OF FINDINGS FOR ASBESTOS EXPOSURE BY POTENTIAL LATENCY¹ AND DECADE OF ENTRY

POTENTIAL LATENCY	MEAN POTENTIAL ASBESTOS EXPOSURE (MONTHS)	% EXPOSED	OR	CHI
1. 40 years cases controls	41 18	13/28 = 46% 46/165 = 28%	2.24	3.88
2. 30-39 years cases controls	41 56	5/10 = 50% 6/12 = 50%	1.0	-
3. 20-29 years cases controls	6 18	6/14 = 35% 6/20 = 30%	1.29	0.14
Entry Decade				
1. <1930 cases controls	41 18	16/32 = 50% 28/101 = 28%	2.61	5.21
2. >1930 cases controls	17 22	13/20 = 35% 30/96 = 31%	1.18	0.11

¹Latency defined as Year Out - Year In.

TABLE 99 (cont'd)

SUMMARY OF FINDINGS FOR ASBESTOS EXPOSURE BY POTENTIAL LATENCY¹ AND DECADE OF ENTRY

POTENTIAL LATENCY	% FOREIGN BORN	MEAN TOTAL ACTIVE DURATION	MEAN AGE AT HIRE	MEAN AGE AT DEATH
1. 40 years				
cases	25	409	26	73
controls	22	350	31	-
2. 30-39 years				
cases	20	326	28	63
controls	33	242	40	-
3. 20-29 years				
cases	30	204	45	70
controls	20	171	47	-
Entry Decade				
1. <1930				
cases	25	399	26	72
controls	25	386	28	-
2. >1930				
cases	25	240	40	72
controls	20	260	39	-

¹Latency defined as Year Out - Year In.

DISCUSSION

This investigation explored the possible work-related excess of stomach cancer, while controlling for as many non-occupational confounders as possible and Table 100 summarizes all findings not directly related to the OT analyses. Because of the nature of the analyses we used (mostly odds ratios and t-tests), it was necessary to assign individuals to either an exposed or unexposed group, regardless of which of the chemical groups was being investigated. The central limiting factor, however, in all investigations conducted at the OHSG, and indeed in much of occupational research, concerns the validity of these exposure classifications, which often involve arbitrary decisions. While these arbitrary decisions are certainly based on reasonable approximations to the truth, it becomes necessary to make rather extensive generalizations and assumptions. There is also much room for subjectivity and error, and both of these factors may lead to misclassification and loss of validity.

Exposure classification for all analytic studies conducted to date at the OHSG is based on the Occupational Title (OT) system. This system condenses the thousands of jobs within the rubber industry into approximately 100 OTs which share common production processes. It should be noted that this system does not claim to be based on specific exposures, although the assumption is often made that common production processes can be equated with common exposures. This equation is, at

TABLE 100

SUMMARY OF MAJOR FINDINGS NOT DIRECTLY RELATED TO EXPOSURES

1. Marital Status

Slightly higher proportion of separated, widowed or divorced in Company A; no difference in Company B.

2. Education

No significant differences in either company.

3. Birthplace

Slightly greater proportion of cases were foreign-born in each company, with a greater discrepancy in Company B.

4. Calendar Year of Hire

Earlier year of hire for Company A; no difference for Company B. Difference in Company A confined to comparison of cases with ARSD-matched controls.

5. Age at Hire

No difference for Company B; slightly younger age at hire for cases in Company A, with difference confined to comparison of cases with ARSD-matched controls.

6. Total Duration in Active OTs

No difference for Company B; slightly longer duration for Company A cases, with difference confined to ARSD comparison.

best, moot. We note, however, that even two individuals performing the same job can differ considerably in their exposure to toxic substances by virtue of the precise manner in which they perform their jobs, much as two smokers who consume the same number of cigarettes may differ considerably in the amount of carcinogen they inhale by virtue of their style of smoking.

The difficulty in assessing exposures and exposure levels, therefore, begins at the level of the individual and is compounded at each step of the decision process, which results in ever broader classifications. At the OT level, we may be dealing with a category which includes perhaps fifty different jobs in more than one area of the plant, with obvious inherent difficulties regarding assumptions that all individuals in this OT are subject to the same exposures. These difficulties are further compounded by the next categorization, which involves condensing the 100 OTs into a more manageable number of perhaps twenty, which are more easily handled in analyses.

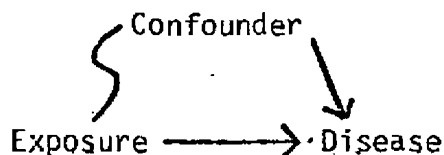
What we have, therefore, is a system which requires, at every step, ever broader classification schemes and ever more general assumptions which may be drifting further and further from truth, all of which may lead to serious loss of validity. To further confuse the issue, we assume in our system that a surrogate for dose is estimated by duration of employment within an OT, already having assumed that all individuals have the same exposure dose for one days' work, and that this exposure has not temporally changed so that whether the exposure occurred in 1930 or 1970, they are qualitatively and quantitatively similar.

Despite these limitations, it must immediately be added that the system in use at the OHSU is probably as good as any other available for hypothesis generation in occupational studies. After all, any large industry demands the performance of very many diverse jobs and the investigator is faced with the problem of condensing this large number into a small number of meaningful subgroups, the classification being based on the particular investigation being conducted. While the creation of these groups is difficult enough even when a specific hypothesis is being tested, it becomes overwhelmingly difficult when the investigator is engaged in a hypothesis-generating endeavor where he essentially admits that he is uncertain about the nature of the agent which he believes is responsible for an excess of some disease. In this investigation, both approaches, hypothesis testing and generating, were used, although the study should be considered mainly of the hypothesis-generating type. For the hypothesis generating portion of the study, we used twenty-one more or less standard OTGs used in other investigations, with the hope of uncovering some high risk area which could then be more fully explored in terms of specific exposures within these areas. Because of the possible existence, within the industry, of four specific agents or classes of chemicals (nitrosamines, polycyclic hydrocarbons, talc containing asbestos, and carbon black) implicated as possible etiologic factors in the development of gastric malignancies, we created specific OTGs for these chemicals. For each chemical, we created four OTGs with potential for high, moderate, low, and no exposure based on an ordinal exposure scale ranging from 0 to 3. Each of three industrial

scientists at OHSG (Messrs Arp, Gamble and Williams) independently evaluated each OT and determined where each of these four classes of chemicals would have been used or generated within the industry if they were present at all, and this was done for the broad time frame 1915-1970, based on which an exposure score was assigned. These scores were then averaged, following which the exposure categories were created and analyzed. We have, therefore, a system of exposure classification which, while imperfect, nevertheless has a reasonable inter-observer reliability and can be considered an approximation to definitive exposure indices.

Now that we have considered the validity of the exposure classification, or external validity, we should turn our attention to the question of internal validity, or the validity of the specific comparison of cases with controls and of the conclusion based on these comparisons. The essence of internal validity involves the unbiased nature of the estimate of effect which is said to be biased (from lack of internal validity) if the estimate is inaccurate because one or the other of the comparison groups has certain attributes which can affect the outcome and which are differentially distributed between the groups. That is, the outcome is being affected in a differential way by this attribute so that the estimate of effect, which is based on an internal comparison (e.g. rate among exposed vs. rate among the unexposed) is no longer accurate or valid, this being an issue of internal validity. The attribute referred to is generally called a confounding factor because its existence confounds or obscures the relationship of interest, destroys internal validity, and leads to a biased estimate of effect.

A confounder can be conceptualized as a predictor or alternate cause of the outcome under study and it must be differentially distributed among the groups being compared for the estimate of effect to be biased. This can be presented diagrammatically as



In other words, a factor is a confounder if it is distributed differently among the groups being compared (exposed and unexposed) while it is predictive of the disease in each group separately (or independent of exposure). The former condition is represented by a squiggle while the latter is represented by an arrow. For instance, if one conducts a ten year lung cancer cohort study where members of the exposed group are all young while the unexposed group is older, we can expect to find a higher lung cancer rate among the unexposed than would otherwise have occurred simply because they are older than the exposed group and age is predictive of lung cancer among both smokers and non-smokers. Unless this difference is controlled for, the estimate of the effect of smoking on the incidence of lung cancer will be biased due to confounding by age. The most widely used methods for the control of confounding include matching in the design, stratification on the confounder in the analysis, or use of multivariate analytic techniques such as multiple regression or analysis of covariance.

Investigators often assume that certain factors, most commonly age, race, and sex, are "universal" confounders, meaning that they will confound any investigation undertaken. To prevent this potential loss

of internal validity, therefore, subjects are matched on these characteristics during the subject selection phase of the study. Methodologists often stress, however, despite this "universal" assumption, that a factor is a confounder only if it is a confounder in the data for the specific study being conducted. If one accepts this admonition in a practical way, one would never match during the design of any study. We, on the other hand, felt that it was reasonable to assume that differences in the age, race, and sex of subjects would lead to a biased estimate of effect in our study since it did so in virtually all reviewed studies of stomach cancer.

In addition to matching on these three attributes, we matched one of the control groups (ARSD) on total duration of employment as well, because we felt we had to provide equal opportunity for all subjects to have worked in all OTs. If we had not provided this equal opportunity, it could have been argued, on finding an elevated odds ratio, that the explanation lies not with some disease-related exposure but that the elevated ratio could be function of the greater length of time spent by the group under study within the industry. To circumvent this additional problem in data interpretation, therefore, we matched one group on this factor, using the difference between the seniority date and the last date worked as an estimate of total duration of employment.

When a determination was made, however, of the total duration of employment within active OTs for each of the two control groups, there was no statistically significant difference between the two control groups in this modified duration. In essence, therefore, we had four controls

for each case matched either directly or indirectly on age, race, sex, and duration of employment in active OTs. The absence of any difference between the two control groups is probably explained on the basis of the age match; most workers within the rubber industry begin their employment at a relatively young age (approximately 30) and spend most of their productive lives within the industry. Having matched on age (year of birth and age at death), therefore, we have apparently indirectly matched on duration of employment as well. This finding may, however, also be explained by the long latency of the disease and the common practice of working until retirement age, with the combination of these two factors responsible for the similar durations of employment, and this would have occurred even without matching.

Because the two control groups had similar total active durations, and these durations did not significantly differ from the durations of the cases, the original plan calling for the termination of the work history of controls when they had attained a duration equal to that of the case was ignored. For most analyses, therefore, data from all controls were pooled and no artificial termination of work experience was executed. While those similarities in duration simplified the analyses, however, it should be borne in mind that we lost the opportunity to test the hypothesis of a generalized effect, which would have been evidence by a difference in duration between cases and comparands. Having matched indirectly on duration, the opportunity to test this hypothesis disappeared. While on this subject of indirect matching, it should also be noted that there were no consistent statistically significant differences between cases and

controls for year of hire and age at hire and this, also, may have been caused by indirect matching.

At this point, a word about the analysis is in order. Because we avoided many confounders by matching during subject selection, we were forced to utilize specific analytic procedures, such as Mantel-Haenszel Odds Ratios and Paired T-Tests, which maintain the integrity of the matched sets (or stata). Referring back to the diagram of a confounder, we see that since the confounder is itself a predictor, or alternate cause, of the disease (or outcome), the exposed and unexposed groups can be expected to have, because they were matched on numerous true confounders, outcomes which are more similar to one another than would otherwise have occurred had they not been matched on these factors. That is, matching on true confounders decreases the difference in outcome between the two groups by reducing the variance in the measure of effect and hence increasing the precision of this estimate. As a consequence, matched analyses can be conceptualized, although not in a strictly mathematical sense, as procedures which take into account this smaller difference, thereby permitting the conclusion of a statistically significant difference between the groups being compared, even though this difference may be smaller than would otherwise be necessary for concluding that a significant difference exists.

While use of an appropriate analytic procedure maintains the integrity of the matched sets, however, there are fewer of those procedures available and they are often computationally more difficult to use. For this reason alone, investigators should carefully consider all aspects of this

study before making a decision regarding matching in the design. Alternative methods for control of confounding, such as stratification in the analysis (which was used for numerous confounders in this study) or subject selection restriction (which was not used) should be extensively weighed before any conclusions are made, since an ideal design is not much use without the appropriate techniques for analysis, especially when the questions being asked are rather complicated and require sophisticated analytic procedures.

While it is obvious from reading this report that most of the analyses presented maintained the matching, we did occasionally avail ourselves of unmatched analyses. For instance, in examining the odds ratios separately for foreign and native born cases, it would be counter-productive to maintain the matching, since matched controls may or may not have the same birthplace as the case, which means that we might be comparing odds ratios for foreign born cases and native born controls, or vice versa, which would defeat the purpose of the analysis, in which instance dissolution of the matching would be the more appropriate analytic technique.

At this point, before discussing the results of this investigation, it would be in order to present some possible limitations, aside from the difficulty of determining true exposures, of this study. First consideration must be given to the fact that case identification for this study relied upon mortality from, and not the incidence of, stomach cancer. While we have great confidence in our follow-up of the large cohorts studied at OHSU (approximately 95%), and despite the fact that

the median survival time for stomach cancer is less than half a year, the possibility nevertheless exists that we have systematically missed the younger and/or less severe cases with the greatest chance for survival, especially but not exclusively since the cohort from which the cases were derived required that all members be forty years of age or greater at inception of the study. These cases, if they exist, may indeed be qualitatively different, and may have had different exposures, from those which were included in this study.

In addition to this possible limitation concerning cases, it should also be noted that there was no check of the hospital records of controls, so the exclusion of individuals as eligible controls because of malignancies was based entirely on the conditions listed on the death certificates. Indeed, one may even question the validity of excluding all individuals with malignancies from the comparand pool, since there is certainly no evidence that all malignancies are associated with the same exposures as those believed to be responsible for the excess mortality from gastric cancer. And one must also consider that by excluding malignancies from eligibility, we have "forced" most of the deceased controls to have died from either heart disease or stroke, the two conditions which, along with cancer, are responsible for the great majority of deaths in this country. And, if those controls who died of cardiovascular diseases happen to have exposures similar to those with stomach cancer, for whatever reason, we are faced with estimates of effect (exposure) biased towards the null and hence loss of validity. Restrictions regarding control selection, therefore, are, and will

probably always remain, debatable regardless of which criteria are employed.

Three final brief points should be made at this time regarding this project study. First, while there was a considerable effort expended to determine the Socio-economic status (SES) of subjects in this study from evaluations of each job by the industry, on which their pay scale was at least partly based, there were problems with this analysis which precluded its inclusion in the present study. While we do not expect much variation in SES among blue-collar workers, and analysis of educational attainments did not reveal any differences between cases and controls, this factor is important in the study of stomach cancer. Second, there is evidence that the relative risk of developing stomach cancer for smokers compared with non-smokers is approximately 1.3, and the same may be true for alcohol consumption. Since we were unable to determine smoking and drinking histories the possibility exists that there was a higher proportion of smokers or drinkers among cases, which could explain part of the excess. Third, the nativity factor is of major importance in the study of stomach cancer and even second and perhaps third (this is just now being extensively studied among migrants from Japan) generation Americans, born of parents or grandparents from high risk countries, continue to experience excess mortality from stomach cancer. Since we were only able to determine the nativity of the subjects included in this investigation, and not the nativity of their forebearers, there may have been differences which contributed to the excess disease.

Occupational Associations

The most consistent finding in this study is the very general observation that there is not much difference, in either occupational or non-occupational factors, between cases and comparands in Company B, while there are some differences in the comparisons of Company A cases and controls.

We found, among Company A subjects, that cases had worked in active OTs slightly longer than controls (375 vs. 338 months), and this difference was significant in the comparison with one (ARSD) of the two control groups. We also found that cases started at a slightly (1.5 years) younger age and slightly earlier (1.5 years) than their matched controls, this latter difference being statistically significant for the comparison with one of the control groups although most of these differences were traced to the group of cases entering during the first decade of plant operation. The differences between Company B cases and controls were generally less pronounced, and not statistically significant as well, although slight differences often were found. In addition to these factors, a higher proportion of Company A cases were foreign-born, although a greater proportion of controls were foreign born as well.

The analysis of occupational exposures was based on two different exposure classification systems - one using "standard" OTGs based on similar aspects of production and not necessarily on common exposures, and the second based on the potential for specific chemical exposures, a system developed exclusively for this study and based on a review of the literature, including both human and animal studies, from which were

derived a list of chemicals - aromatic hydrocarbons, nitrosamines, asbestos, and carbon black, the latter possibly being a carcinogen in its own right or a particulate to which the polycyclics may be absorbed - whose association with stomach cancer appeared regularly in the literature and which were used as raw materials, or generated by industrial processes, within the industry.

The creation of the chemical-specific high risk OTGs, as described earlier in this chapter, was based on three independent assessments of the levels of these chemicals within each of the OTs, and those assessments were made by the three OHSO environmentalists most knowledgeable about these matters. While they are based on extensive experience, they must, in the end, be considered at least partially subjective to varying degrees, (as will soon be explained) and they do not escape the limitations of the OT system.

The reference to varying subjectivity must be further discussed here. One of the groups, the nitrosamines, are not used as raw materials per se and an estimate of their probable levels is therefore based on a judgement concerning where they might be generated although in principle one can sample for a precise determination of levels. Aromatic hydrocarbons, as well, are not used in raw form, although they may be contaminants of some commonly used solvents. Considerable knowledge is presently available concerning the use of these solvents within different OTs. The determination of carbon black levels is rather direct because we know exactly what it does, and where it is used, in addition to being visible. Assessment of asbestos levels, on the other hand, are indirect because they are based on the presence and use of anti-sticking (detackifying)

agents which are most often talc or soapstone although other agents, such as mica, or even cornstarch, are also used, depending on costs at the time of purchase. The most used agent, however, is believed to be talc, and this substance is believed to contain asbestiform material to varying degrees. Despite the assumption on which asbestos-level determinations are based, however, talc, like carbon black, is visible and its use within the industry is reasonably well documented.

An examination of the results from the standard OTG classification system did not reveal any pattern of consistently elevated odds ratios, with most elevations being generally scattered throughout the earlier end of the industrial process and being found in the following OTGs - Calendering, Tuber, Tire and Bead Fabrication, Tube Fabrication, Cure Preparation, and Curing. While there was no striking consistency to these findings, it is interesting to note that these OTGs generally have high dust levels, consisting mostly of talc or other detackifiers, and also use solvents extensively, the latter being possibly contaminated with polycyclic hydrocarbons.

The most provocative finding occurred when using the chemical-specific OTG classification, which indicated significantly elevated odds ratios for potential exposure to high or moderate talc levels, with the ratios being significantly elevated for exposure on an ever-never basis, as well as for exposure of two, five, and ten years

duration, each compared with no exposure at all. While these statistically significantly elevated ratios are not independent of one another, since subjects with ten years of exposure are included in the other three groups, the consistency was nevertheless striking. This finding pertains only to Company A, however, and the similar analysis conducted within Company B indicated interestingly, that the odds ratios were significantly low, a finding which may be attributed to random fluctuations and not to some underlying protective elements within these OTs. Equally, and perhaps more likely, may be selective out-migration from dusty areas, a reasonable explanation only if company policies and practices differed in regard to selective job changes.

In addition to these findings of statistically significantly elevated odds ratios within Company A, we have additional evidence for the association of stomach cancer with OTs high in probable talc (or detackifier) exposures from the T-Test utilizing durations of employment within these OTs, which indicated significantly more time (forty-nine versus twenty-five months) spent in these OTs by the cases, and the additional finding that the exposures among the cases occurred earlier than it did among the controls when dust levels may have been higher.

Since there was a question concerning the possible causal effects of the slightly younger age and earlier calendar year of entry into the industry for cases in comparison with ARSD-matched controls, separate T-Tests and Odds ratios for asbestos exposure were calculated for this group, as well as for the ARS-matched controls. The T-Tests results, described in the previous chapter, indicated virtually no difference in duration of exposure for the two groups and the ORs were similar.

The combination of those findings demonstrates the existence of an association between stomach cancer and dusty areas in which talc may have been used and which could have been ingested via capture by mucus in the nasopharynx or by expectoration and subsequent swallowing, a mechanism postulated by numerous investigators for the ingestion of particulates.

Because of the earlier finding of a disproportionate number of early entry cases, separate analyses by decade of entry and by latency period were performed, the latter based on the difference between year of death and year of hire, on the assumption that low-level exposures began during the first year within the industry. These analyses were unmatched and indicated that the odds ratios for potential asbestos exposure were elevated for the earlier decades and longer latency periods, with the OR for a latency of 40 or more years significantly elevated (OR = 2.24) while the ratio for entry prior to 1930 (OR = 2.61) was also significantly elevated. It appears, therefore, that much of the excess can be statistically attributed to those individuals who began working in the industry quite early, at which time the dust (and hence potential asbestos) exposure may have been higher than the levels during later years. This is further confirmed by the fact that the group with the 40 year potential latency first entered a high talc OT, on the average in 1930, while controls with a similar potential latency had a mean first entry year of 1937. The medians for these two groups were 1926 and 1936, respectively. From an examination of Table 97, we observe a clearly decreasing gradient of mean exposure among exposed cases, but this same gradient does not exist among controls. In fact, only among those with

the longest potential latency do we observe longer exposures among cases. From these decade of entry and latency analyses, therefore, it appears that the excess of deaths from stomach cancer is attributable to a combination of earlier and longer exposures.

The attributable risk per cent (among the exposed) (OR-1/OR multiplied by the proportion of cases exposed) for this exposure, using an odds ratio of 2.5 and a case exposure proportion of fifty-two percent (27/52) is calculated to be thirty-one percent, which indicates overall that the occurrence of thirty-one percent of the fifty-two cases, or approximately sixteen cases, can be attributed to detackifier exposure assuming no bias or random measurement errors. Similar calculations are not presented for Company B, naturally, since no association was demonstrated.

In view of the fact that the point estimates of the SMR, on which these studies are based, were one-hundred eighty-seven and one-hundred twenty-four for Companies A and B, respectively, and considering that the published Company A SMR (135) was presented as being statistically significantly elevated while the published Company B SMR (136) was not, it appears that the absence of a statistically significant excess in Company B is confirmed by the absence of any consistent findings for that company in this study, while the significant excess among Company A subjects is confirmed by our analysis and may be largely explained by a history of working in areas with probable exposure to anti-sticking agents, mostly talc. Because of the presumed contamination of talc with asbestos, especially in earlier calendar periods, there is a fairly strong possibility that this involved asbestos exposure as well. In Company A, we observed fifty-two cases and expected twenty-eight, and

of the twenty-four excess deaths, sixteen appear to be attributable to employment within OTs thought to contain high levels of asbestos. These findings, therefore, appear to explain most of the observed excess.

Suggestions for Further Research

First consideration for further research must be given to the creation of a classification system based directly on exposures. Such a system is presently being developed here at the OHSG and is being based on a grid system in which workers in close physical proximity to each other are grouped together. While this system is very promising, it will probably not be appropriate for retrospective use, which means that the present OT system is the only, and therefore the best, available. Since we are now entering the surveillance phase of our activities, however, every effort should be made to refine this new system as quickly as possible.

The data on which our conclusions are based in this present study would doubtless have been better if we had knowledge concerning the actual dose of exposure, and not just the amount of time spent in the various OTs. If these levels can be reconstructed, perhaps from purchasing records, re-analysis with this additional factor, would be appropriate. It would be especially interesting to compare samples of Company A and B talc (or detackifiers) collected when most exposures in this study (1915-1950) occurred or, in lieu of this, to trace the suppliers, and from this to reconstruct the asbestos levels within these products.

In addition to further analysis of the asbestos levels, it would be appropriate to further examine these data for a determination of the historical periods during which both cases and controls were exposed to solvents, since there is some suggestion in our data concerning an association between stomach cancer and solvents and since the purity of the solvents and hence possible contamination by polycyclic hydrocarbons apparently changed significantly around 1940. Since expectoration and subsequent ingestion or via the mucus system is the presumed mechanism, it would be very interesting to examine those OTs associated with both chronic pulmonary diseases and high asbestos levels, since the former may cause a greater frequency of expectoration, and hence of ingestion.

It would also be desirable to perform a more detailed analysis of the specific exposures which occurred during the estimated latency period (twenty-forty years) for stomach cancer, although the variability in the estimate of this latency period is great and the period itself is long.

Finally, in view of the many factors, both occupational and non-occupational, which may be associated with the incidence of stomach cancer, such as nativity, socio-economic status, and age and calendar year at hire, among others, it would probably be best to control for all of these factors simultaneously by the use of an appropriate technique, such as, perhaps, the confounder summarization score.

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APPENDIX I

OCCUPATIONAL TITLES

Number	Code	OT
001	BPTR	Batch Preparation-Tires
002	BPTU	Batch Preparation-Tubes, Flaps, & Bladders
003	PIDE	Pigment Blending
004	CENC	Cement Mixing
005	CNTR	Cutting & Milling-Tires
006	CNTU	Cutting & Milling-Tubes
007	SBPR	Service-Batch Preparation-Tires
008	SBPU	Service-Batch Preparation-Tubes
009	MITD	Milling-Treads
010	MIPL	Milling-Plystock
011	MIFB	Milling-Flaps & Bladders
012	MITU	Milling-Tubes
013	MIMS	Milling-Miscellaneous
014	CALO	Calender Operation
015	CALT	Calender Tending
016	SRLC	Roll Changing-incl. Trucking & Service
017	PLHA	Plystock Handling-incl. Bead Building
018	SLIN	Liner Service (reroll, mend, clean)
019	TUBD	Tuber Operation-Treads
020	TUEU	Tuber Operation-Tubes
021	TUBC	Tuber Operation-Flaps & Bladders
022	STTU	Tuber Service-Tubes
023	STOX	Tuber Service-Flaps & Bladders
024	STOD	Tuber Service-Tread Tuber (incl. booking & slitting)
025	CEMD	Cementing-Treads
026	BEEL	Bead Building
027	TRBL	Tire Building
028	STEB	Service-Tire & Bead Building
029	INRE	Inspection, Repair, & Sort Green Tires (incl. trucking)
030	PALI	Paint & Line-Green Tires
031	VVMA	Valve Preparation
032	FUSP	Tube & Flap Building
033	CRTR	Curing-Tires
034	CRTU	Curing-Tubes
035	CRFB	Curing-Flaps (black)
036	CRFW	Curing-Flaps (white)
037	CRBA	Curing-Bladders
038	CRVV	Curing-Valves
039	SMOL	Mold Cleaning & Repair
040	FIRA	Finishing & Inspecting-Tires
041	FIRE	Repairing Tires
042	FITU	Finishing & Repairing-Tubes & Airbags
043	FINX	Finishing & Repairing-Flaps, Bladders, & Sleeves
044	MNPT	Maintenance-Painting
045	MNWR	Maintenance-Millwright
046	MNEL	Maintenance-Electrical
047	MNSM	Maintenance-Sheet Metal
048	MNWL	Maintenance-Welding
049	MNEC	Mechanic
050	MNCP	Carpentry
051	MNMA	Machinist
052	MNMS	Maintenance-Misc. (pipefitters, cement finisher, etc.)

Number	Code	QT
053	PWPT	Power Plant
054	TEST	Quality Control Testing
055	TCKR	Trucking (genl.)
056	CLRK	Clerical
057	SJAN	Janitor
058	STOR	Shipping & Receiving
059	OTHR	Other Rubber Worker (tires & tubes)
060	MMHC	Mill Mixing
061	RQPR	Prep.-Reclaim
062	RQDV	Devulcanizing-Reclaim
063	RQML	Milling-Reclaim (refining)
064	SRIC	Service-Reclaim
065	SBRP	Service-BB-Misc.
066	CNGP	Cpd. & Mix-Chem. Prod.
067	KOCP	Reaction Opr.-Chem. Prod.
068	FICP	Finishing (dry, bag)-Chem. Prod.
069	SRCP	Ship. & Rec.-Chem. Prod.
070	FOAM	Manufacture Foam Prod.
071	ROCK	Rocket Liner Mfg.
072	URET	Urethane
073	PLST	Vinyl Prod. Mfg.
074	RSMF	Resin Prod. Mfg. (chenigum, pliolite, dispersite) 345A split
075	PFMX	Pliofilm Mixing
076	PEFB	Pliofilm Fabrication
077	PFFN	Pliofilm Finishing
078	BPNC	Batch Prep.-Ind. Prod.
079	INDA	Prep.-Thd. Prod.
080	CRSX	Curing-Ind. Prod.
081	INDC	Finish & Inspect-Ind. Prod.
082	OTNT	Other Rubber Worker-(non-tire & tube)
083	BPNC	Batch Prep.-Hose & Belt
084	INDA	Fabrication-Hose & Belt
085	CRSX	Curing-Hose & Belt
086	INDC	Finish & Inspect-Hose & Belt
087	REDE	Special Rubber Prod. Development (381A & 357A)
088	OTHR	Other Worker (non-rubber-such as police, cafeteria, etc.)
089	SYNT	Batch Prep.-Synthetic Latex
090	SYNT	Preparation & Reaction-Synthetic Latex
091	SYNT	Finishing & Packing-Synthetic Latex
092	METL	Rim Plant-Metal Treatment
093	MECH	Rim Plant-Forming & Machining
094	SPCP	Rim Plant-Welding
095	RPFI	Rim Plant-Finishing & Inspecting
096	PLST	Plastics-Production & Manufacture
097	FUCE	Fuel Cell
098	ARSP	Aerospace
099	METL	Metal Preparation-(mostly degreasing operations)
100	MECH	Mechanical Building
101	SALA	Salary
102	UNKN	Unknown
103	INAC	Inactive File
104	RETI	Retired
105	SICK	Sick Suspense
106	LOFF	Layoff
107	ACTV	Active
108	DEAD	Dead
109	LOAD	Leave of Absence

Number	Code	Of
110	MSAB	Misc. Absence
111	ANOD	Anode Process (Coagulation dip)
112	RBPR	Rubber Preparation
113	RETR	Retread
114	ADHE	Adhesives
115	EXIT	Exit From Work for Other Reasons
116	DRET	Disability Retirement
117	MILT	Absence for Military Service
118	TBCR	Tube Building & Curing
119	FOOT	Footwear
120	RCIP	Reclaim-Industrial Products
121	PWSV	Prior Work With Solvents or Solvent-Containing Materials
122	PWRF	Prior Work With Radio Frequency Energies or Energy Emitting Devices
123	PWDA	Prior Work With Known Dermatitis Producing Agents or Environment Commonly Associated With Dermatitis Problems (Excluding Solvents)
124	PWMF	Prior Work With Metal Fume
125	PWNR	Prior Work Experience Shows No Potential Exposures Relevant To This Study

O. T. Dictionary

<u>OI Code</u>	<u>Occupational Title</u>	<u>Description</u>
BEBL	Bead Building	This involves all processes associated with building beads.
BPTR	Batch Preparation-Tires	Mixing of rubber, accelerators, antioxidants, filters, etc. in banburys. Includes B.B. operators and helpers.
BPTU	Batch Preparation-Tubes	Same as OI except for tubes, flaps, and bladders.
CALO	Calender operation	This O.T. is for those individuals who operate the calenders.
CALT	Calender tending	This includes individuals that assist the calender operator (1st & 2nd helpers), and in the Firestone O.T.'s those on dip operations as well.
CEND	Cementing-Treads	After the treads are cut to the proper size, the cut edges have cement put on them so when the tire builders put the tread on the green tire they will stick together.
CENG	Cement Mixing	Mixing of liquid material (mostly solvents) for use throughout the plant.
CLRK	Clerical	
CNTR	Cutting & Milling-Tires	After internal mixing in the BB, the batch is milled into long sheets, dried and then cut into long sheets and stacked, or pelletized. The pellets or sheets are then either returned to the BB, or milled preparatory to further use (calender for plystock, tuber for treads).
CNTU	Cutting & Milling-Tubes	Same as CNTR only the stock is for tubes, flaps or bladders.
CRBA	Curing-bladders	

GI Code	Occupational Title	Description
CRFB	Curing-flaps (black)	Mold press cure of flaps
CRWH	Curing-flaps (white)	Pot heater cure of talc coated flaps
CRSX	Miscellaneous Curing	Industrial Products
CRTR	Curing-tubes	
CRVY	Curing-valves	
FINX	Finishing & Repairing - Flaps, bladders & sleeves	Same as FITU except for flaps bladders and sleeves.
FIRA	Finishing & Inspecting - Tires	Trim, balance, label, tube & inflate, service, force grind and classify cured tires.
FIRB	Repairing tires	Repair, buff, rag, rib dress, cure repairs of cured tires.
FITU	Finishing & Repairing - Tubes and Airbags	Final inspection and repair of tubes and airbags.
FUSP	Tube and flap building	Splicing and booking tubes & flaps.
INRE	Inspection & repair - Green tires	Inspect green tires for defects, and repair, preparatory for curing.
MECH	Mechanical building	Largely machinist type work.
MIFB	Milling-Flaps & Bladders	Same as MITD only the tuber makes slugs for flaps & bladders.
MIMG	Mill Mixing	Similar to Batch preparation except done on mill, i.e. pigments are added by hand onto a mill. This operation has largely been replaced by banburys.
MIMS	Milling - Miscellaneous	This is milling that does not fit any of the above products, or where it is not known what the product is.
MIPL	Milling - plystock	Same as MITD only it is sent to a calender for making plystock, chafers, inner liner, etc.
MITD	Milling - treads	The mixed rubber (with all its additives) is milled so that the rubber is hot and plastic. This tread stock is then sent to a tuber.

OT Cod	Occupational Title	Description
MTTU	Milling - tubes	Same as MTTO only the tuber makes tubes.
MNCP	Mechanic	
MNEC	Carpentry	
MNEI	Maintenance-electrical	
MNMA	Machinist	
MNMS	Maintenance, miscellaneous	Includes pipefitters, cement finishers and other maintenance jobs not included in 44-51.
MNPT	Maintenance - painting	
MNSM	Maintenance - sheet metal	Ventilation ducts, BS collectors, etc.
MNWL	Maintenance - welding	
MNWR	Maintenance - millwright	Machine Repair
OTHR	Others	Jobs not included in above and non-production (guard, waitress, cafeteria helper, etc.).
PALI	Paint & line - green tires	Spray paint onto green tires before curing. Talc is applied to some tires, and treads jammed in others.
PIBE	Pigment blending	Weighing & mixing of pigments (accelerators, antioxidants) for batch building.
PLHA	Plystock handling	This O.T. includes the splicing of material making plystock for tires, and band building.
PWPT	Power Plant	All operations associated with power plant.
RCDV	Devulcanizing - reclaim	Processes of devulcanization (heating, fiber separation, grinding, batch preparation), digestion (batch preparation, digestion, dewatering, drying)
RCMI	Milling - reclaim	Processes of mixing & blending, refining, straining, packaging, extruding, batch building.

Of Code	Occupational Title	Description
RCPR	Preparation - reclaim	Processes of digestion, heating, sorting, cracking, shifting, magnetic separation, collection and storage.
RETR	Retread	
SALA	Salary	
SBPR	Service - Batch Preparation - Tires	Truck materials to BB for mixing (such as tube stock from CHIR to be run through BB a second time, supply mixed pigments ok).
SBPU	Service - Batch Preparation - Tubes	Same as SBPR only for tube, flap, and bladder stock.
SPCP	Special Products	Largely defense products made during WWII.
SJAN	Janitor	Some janitors (e.g. BB cleaners) be in service operations.
SLIN	Liner Service (reroll, mend, clean)	This OT takes the liners in which the plystock is wound into rolls and rerolls it after the plystock is used up by the tire builders, and cleans and mends the liners when necessary.
SMOL	Mold cleaning & repair	Includes trucking of molds to be cleaned
SREC	Service - reclaim	All service operation associated with reclaim operation.
SRLC	Roll changing (including trucking & service)	These are service people involved in plystock preparation. It includes those changing the rolls on the calenders, bias cutting machines, truckers (taking rolls to storage areas), etc.
STBS	Service - tire & bead building	Trucking plystock, tread, inner liners, etc., and materials to tire builders and bead builders.
STOD	Tuber service - tread tuber (including booking & slitting)	Similar to STTU except for tread stock. Includes slitting the treads and putting cemented treads into trays.

Of Code	Occupational title	Description
STOR	Shipping & receiving	All activities of receiving, unloading, packing and loading materials and finished products.
STOX	Tuber service - flaps and bladders	Similar to STTU except for flaps and bladders - cutting slugs, hooker, etc.
STTU	Tuber service - tubes	This would include service operations related to tubers making tubes, such as cutting tubes, punching holes for valves, putting on valves.
SYNT	Synthetic plant	Manufacture of synthetic rubber.
TEST	Quality control testing	All activities associated with quality control (pigments, stocks, tires, tubes, etc.)
TCKR	Trucking (general)	All trucking not included in service jobs above.
TRBL	Tire building	
TUBC	Tuber operation - flaps and bladders	Same as TUBD and TUBU except flaps and bladders are made.
TUBD	Tuber operation - treads	This OT runs the tuber which takes the stock from a mill, puts it through a die forming a tread.
TUBU	Tuber operation - tubes	Similar to TUBD only a tube is formed instead of a tread.
UNKH	Unknown	Do not know enough about the job to put in above OT's, or does not fit above OT's.
VVHA	Valve Preparation	Making, spraying and buffing valves.

OCCUPATIONAL TITLE GROUP DICTIONARY

OIG	GENERAL DESCRIPTION
1 Batch Preparation	Raw ingredients (rubber, fillers, oils, and pigments) are weighed and mixed together in a banbury mixer. Environmental exposures to particulates are high. Component OT's: BPTB, BPTU, PIML, CENG, CMIR, CMTZ, SBPR, SBPU, NING, BPTD, BPMC, RBPB.
2 Milling	Rubber mix from the banburys is processed further under heat and pressure, till the rubber is in a soft, plastic state. Component OT's: MITD, MIPL, MIFB, MITU, MIRS.
3 Calendering	The rubber stock from the mill is rolled out into a sheet of controlled thickness. The plystock is cut and spliced for use in building the ply of the tire. Some exposure to reaction products and solvents exists. Component OT's: CALD, CALT, SRLC, PLHA, SLIN.
4 Tuber	Rubber stock from a mill is forced through a die forming a tread or tube. The tread is cut in appropriate lengths and cemented with solvents on the cut end to provide a tacky surface. Component OT's: TUBD, TUBC, STOX, STOD, CEND.
5 Fabrication - tires and beads	Beads are rubber and fabric-covered wires that rest on the rim of the wheel in a finished tire. Treads, beads and plystock are used to build the tire. Major exposures are to solvents. Component OT's: BEBL, TRBL, STBB.
6 Tubes	The tube from the extruder is cut, valves are attached, and the inside of the tube is coated with talc and then spliced together. Valve making involves adding a rubber patch to the valve. The rubber is then cured, buffed and sprayed with a solvent to make it tacky. Component OT's: TUBH, SYTU, VVMA, FUSP, CRTU, CRVV, FITU.
7 Curing preparation	Spraying green tires or tubes before curing; sorting, repairing and inspecting green tires or tubes before curing. Component OT's: INRE, PALI.
8 Curing	The green uncured product is cured under heat and pressure. Major environmental exposures are to reaction products (curing fumes) and talc. Component OT's: CRTR, CRFB, CRFW, CRBA, CRVV, SMOL.
9 Inspection	The cured tire is inspected (repaired if necessary) and made ready for shipping (finishing). Component OT's: FIRA, FIRB.

OTG	GENERAL DESCRIPTION
10 Maintenance	This OTG includes mechanics, pipefitters, electricians, welders, painters, sheet metal workers and millwrights. Component OT's: MNPT, MNBR, METL, MRSU, MRAA, MTC, MNCP, MNMA, MNMS, PRPT.
11 General Service	This is a miscellaneous group with a variety of different jobs and exposures. Component OT's: TEST, TCRK, CLCK, SJAN, OTHR, OTHP.
12 Shipping & receiving	Receiving, unloading and storing all incoming ingredients that go into making the final product, e.g. carbon black, pigments, raw rubber, etc. Loading the final product into trucks and/or boxcars. Component OT's: STOR.
13 Reclaim	Scrapped, vulcanized rubber products are shredded, ground up, and devulcanized. The rubber compound is restored to its original plastic state through application of heat and chemicals. Primary exposures are to particulates and devulcanizing agents. Component OT's: RCPR, RODY, RCHI, SREC.
14 Chemicals	Chemical products, including synthetic latex (one Akron plant), are compounded, mixed, dried and bagged in this OTG. Component OT's: CMCP, ROCP, FICP, SPCP, RSIF, PFMX, PEFB, PFFN, SYNT.
15 Plastics	Jobs in this group included the manufacturing of foam, urethane and vinyl products with a variety of exposures. Component OT's: FOAM, URET, PLST.
16 Preparation other than tire and tubes	Raw ingredients are compounded and mixed prior to banbury milling. Exposure to particulates are high, especially during and prior to extrusion of tubes. Component OT's: INDA.
17 Final inspection of tubes	The cured tube is inspected (repaired if necessary) and made ready for shipping (finishing). Component OT's: INDC.
18 Metal handling	Rim plant jobs are currently being phased out in Akron. A minimum amount of experimental type jobs involving metal handling and welding offer some, but very little exposure to lubricating oils, solvents, and particulates. Component OT's: METL, MECH, SPCP, PRPT.
19 Other rubber	This OTG includes a variety of different jobs, where products other than tires and tubes are produced: footwear, adhesives and fuel cells, for example. Component OT's: ROCK, OTNT, REDE, FUCE, ARSP, ANOD, ADRE, FOOT.

<u>01G</u>	<u>GENERAL DESCRIPTION</u>
20 Salaried	This 01G includes managerial, secretarial and other office jobs. (Foremen are not included here, rather are assigned to the other 01G's). Component 01's: SALA.
21 Unknown	Not enough information on the work history to assign to specific 01G. Component 01's: UNKN.

SUMMARY OF MAJOR POTENTIAL EXPOSURES TO CHEMICAL AGENTS
IN TIRE MANUFACTURING OTG's

Compounding and Mixing	Accelerators, (e.g., thiazoles, guanidines, thiuram sulfides, carbamates). Antioxidants Fillers (carbon black) Extender
Cutting and Milling	Talc
Milling	*Emission from Vulcanization Process
Extrusion	Solvents
Calendering	*Emissions from Vulcanization Process
Tire Building	Solvents
Curing Preparation	Variable exposure to solvents, talc
Curing	*Emission from Vulcanization Products
Final Inspection	Cured rubber dust, solvents

*Emissions from the hot rubber mix can be of two sorts (based on theoretical considerations), and will not be the same for milling, calendering and curing.

1. Volatization -

- a. Residual monomers (probably only milling and calendering)
styrene, acrylonitrile, chloroprene
- b. Antioxidants and Antiozonants and Accelerators - higher loss in milling and calendering
- c. Processing Aids - oils
- d. Miscellaneous Ingredients - special ingredients (amines, esters, organic acids) and impurities (5-40% of main ingredient).

2. Formation of New Compounds - Oxidative products are formed in milling and calendering; reductive products are formed in the mold during curing, oxidative products when the curing press is opened. The compound classes formed include amines and ammonia, organic sulfides, hydrocarbons, acids, esters, water.

It has been estimated that 0.5-0.7% volatile material would be released and conceivably 1,000 or more different compounds.

APPENDIX II

APPENDIX II

PG2
OHSG COMPUTER GROUP
UPDATE 0
MAY, 1977

VARIABLE CASE-CONTROL STUDY PROGRAM

OCCUPATIONAL HEALTH STUDIES GROUP
SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF NORTH CAROLINA
CHAPEL HILL, NORTH CAROLINA 27514

1.0 GENERAL DESCRIPTION

1.1 ABSTRACT

The Variable Case-Control Study program is designed to produce statistics for case-control studies when either a fixed or a variable number of controls are matched to the cases in a file. The statistics may be generated for one or more fields in the records and they are:

1. odds ratio
2. Chisq
3. Chi
4. Confidence Interval

1.2 SOURCE

Allan Smith (Department of Epidemiology) requested the development of this program, supplied the formulas, and also participated in the documentation. It is an expansion of an earlier OHSG program designed by Ravi Mathew (Programmer) and Professor Anthony McMichael (Department of Epidemiology) which analyzed case-control files that had a fixed number of controls matched to a case.

1.3 COMPUTATIONAL PROCEDURE

For case-control studies, a case record and the one or more control records that are matched to that case make up a single entity for analysis purposes. For these groups, formulas have been developed which uses a 2-by-2 matrix as the basic component for solving the equations. The matrix contains exposure information on a field to be analyzed.

2-by-2 Matrix

	Exposed	Not Exposed	
Case	A_i	B_i	W_i
Control	C_i	D_i	X_i
	U_i	V_i	Y_i

where: i = a group which consists of a single case and
the controls that are matched to that case.

A_i = 1 if the case is exposed and 0 if unexposed.

B_i = 1 if the case is not exposed and 0 if exposed.

C_i = The number of controls exposed.

D_i = The number of controls not exposed.

U_i = The sum of $A_i + C_i$.

V_i = The sum of $B_i + D_i$.

W_i = The sum of $A_i + B_i$.

X_i = The sum of $C_i + D_i$.

Y_i = The sum of $U_i + V_i$ or the sum of $W_i + X_i$.

Formulas based on the 2-by-2 matrix

$$\text{Odds Ratio} = \frac{\sum_i \left(\frac{A_i D_i}{Y_i} \right)}{\sum_i \left(\frac{B_i C_i}{Y_i} \right)}$$

$$\text{Chisq} = \frac{\left(\sum_i A_i - \sum_i \left(\frac{U_i W_i}{Y_i} \right) \right)^2}{\sum_i \left(\frac{U_i Y_i W_i X_i}{Y_i^2 (Y_i - 1)} \right)}$$

$$\text{Chi} = \sqrt{\text{Chisq}}$$

$$\text{Confidence Interval} = \text{Exp} \left(\left(\text{in (odd ratio)} \right) \left(1 \pm \frac{Z \text{ value}}{\text{Chi}} \right) \right)$$

where Z value for normal distribution is 1.96 for a 95% confidence limit and 1.645 for a 90% confidence limit.

There can be more than one field in the Data records for which the analysis is desired and the concept of the 2-by-2 matrix would have to be produced for each of them. The program will treat all blanks or zero as not exposed and treat any other value in a field as exposed. Changing of values to meet these criteria must take place outside of this program, if necessary.

2.0 INSTRUCTIONS FOR USE

2.1 ORDER OF JOB DECK

```
//JOBNAME JOB UNC.OHS ..... REST OF JOB CARD .....
//*PW=.....PASSWORD.....
// EXEC PGM=CASE
//STEPLIB DD DISP=SHR,DSN=UNC.OHS.F207F.LOAD
//CONTROL DD *
                [CONTROL INFORMATION]
//DATA DD DISP=OLD ..... DEFINITION OF DATA FILE,....
//SYSPRINT DD SYSOUT=A
```

2.2 PREPARATION OF CONTROL CARDS

Card 1.

All of the fields on this card must be numeric, each field must be separated by one or more blanks, and the values must be contained within column 1-79.

1. The length of a DATA record.
2. Location of an ID field in the DATA record which identifies a case and the controls that are matched with that case.
3. Length of the ID field.
4. Location of a case-control-number in the DATA record which identifies an individual record as being a case record or a control record.
5. Length of the case-control-number.
6. The value of the case-control-number which identifies a case.
7. Maximum number of control records that are matched to any one case.
8. Location of the first time-work-field in the DATA record for which an exposure check is to be made.
9. Length of a time-work-field.
10. Number of digits in a time-work-field which denotes a fraction.
11. The number of time-work-fields in a record.
12. The Z-value which is to be used in the confidence interval formula.

Card 2.

This card contains a title which will appear on the print out above the tables generated, it may be alphanumeric, contained in column 1-80, and column 1 must be a non-blank character.

Card 3-N.

These cards contain labels which will appear on the print out identifying the time-work-fields. Their use is optional. If they are not given, the program will label each time-work-field as OT# 1 - OT# N where N is the number of time-work-fields in a record. If they are given, there may be as many put on a card as will fit, there must be one for each time-work-field, they may be alphanumeric and must have a length of 1-8 characters, must be enclosed within quote marks, and each name with its enclosing quote marks must be separated by one or more blanks.

2.3 DATA FILE

The data file must be sorted in ascending order by ID and case-control-number order and there must be a separate record for each case and control as follows:

First case record
Control 1 for the first case record

...

Control N for the first case record
Second case record
Control 1 for the second case record

...

The required fields in a record are:

1. An ID field which identifies a case and the controls which are matched to that case. This field may be alphanumeric and may contain blanks.
2. A case-control-number which identifies a record as being a case or as being a control. This number must be all numeric and cannot contain leading blanks even if more than one digit long.
3. The time-work-fields. These fields may contain blanks, numbers, and a decimal point. If a decimal point is included in the value, it overrides the fractional specification given in the Control cards. If a decimal point is not included in the value, the fractional part is taken to be the number of rightmost digits specified in the Control cards. All of the time-work-field which are to be analyzed must be adjacent to one another.

In order for a group of records having the same ID to be included in the analysis, they must pass the criteria of the above items as well as the following:

1. There must be a case record and some control records for each ID.
2. There cannot be duplicate case numbers or duplicate control numbers for an ID.
3. The value that identifies a record as being a control must be greater than the value that identifies a record as a case.
4. The number of control records matched with any one case cannot exceed the maximum specified in the control cards.

2.4. EXAMPLE EXECUTION

```
//B109 JOB UNC.OHS.F299E,R-LEGGETT
//*PW=9907
// EXEC PGM=CASE
//STEPLIB DD DISP=SHR,DSN=UNC.OHS.F207F.LOAD
//CONTROL DD *
163      5      2      4      1      1      4      23      7      3      5      2.24
B109 Matched analysis on Memphis 1975 data.
'TBLD'    'CADM'    'QRSM'    'TTLD'    'TTLD'
//DATA DD DISP=OLD,DSN=UNC.OHS.F9907.MEMPHIS
//SYSPRINT DD SYSOUT=A
```

3.0 EXECUTION TIMING

The run time used to process 616 records with 21 exposure fields to analysis on each record was 10.8 seconds on an IBM 370/165 computer.

The core storage used was 102K.

APPENDIX III

INTER-OBSERVER AGREEMENT ON ESTIMATE OF POLYCYCLIC HYDROCARBONS LEVELS

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
001 Batch Preparation-Tires	1	1	1		
002 Batch Preparation-Tube, Flaps, Bladders	1	1	1		
003 Pigment Blending	1		2		
004 Cement Mixing		1		2	
005 Cutting & Milling-Tires	1	1		1	
006 Cutting & Milling-Tubes	1	1		1	
007 Service-Batch Preparation-Tires		1	2		
008 Service-Batch Preparation-Tubes		1	2		
009 Milling-Treads		1	2		
010 Milling-Plystock		1	2		
011 Milling-Flaps & Bladders		1	2		
012 Milling-Tubes		1	2		
013 Milling-Miscellaneous		1	2		
014 Calender Operation			2	1	
015 Calender Tending			2	1	
016 Roll Changing-includ. Trucking & Service			1	2	
017 Plystock Handling-includ. Band Building			1	2	
018 Liner Service (reroll, mend, clean)			1	2	
019 Tuber Operation-Treads			2	1	
020 Tuber Operation-Tubes			2	1	
021 Tuber Operation-Flaps & Bladders			2	1	
022 Tuber Service-Tubes			2	1	
023 Tuber Service-Flaps & Bladders			2	1	
024 Tuber Service-Tread Tuber (includ. booking and slitting)			2	1	

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
025 Cementing-Treads			2	1	
026 Bead Building			2	1	
027 Tire Building			2	1	
028 Service-Tire & Bead Building			2	1	
029 Inspection, Repair & Sort Green Tires (includ. trucking)			1	2	
030 Paint & Line-Green Tires				3	
031 Valve Preparation			1	2	
032 Tube & Flap Building			1	2	
033 Curing-Tires	1	1	1		
034 Curing-Tubes	1	1	1		
035 Curing-Flaps (black)	1	1	1		
036 Curing-Flaps (white)	1		1	1	
037 Curing-Bladders	1		2		1
038 Curing-Valves	1	1	1		
039 Mold Cleaning & Repair		1		2	
040 Finishing & Inspecting Tires			1	2	
041 Repairing Tires		1	2		
042 Finishing & Repairing-Tubes & Airbags			2	1	
043 Finishing & Repairing-Flaps, Bladders and Sleeves			2	1	
044 Maintenance-Painting				2	1
045 Maintenance-Millwright				2	1
046 Maintenance-Electrical				2	1
047 Maintenance-Sheet Metal				2	1
048 Maintenance-Welding			1	1	1

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
049 Mechanic				2	1
050 Carpentry				2	1
051 Machinist				2	1
052 Maintenance-Misc. (pipefitters, cement finisher, etc.)				2	1
053 Power Plant			1	2	
054 Quality Control Testing			2	1	
055 Trucking (genl.)			1	1	1
056 Clerical				3	
057 Janitor			1	1	1
058 Shipping & Receiving			2	1	
059 Other Rubber Worker (tires & tubes)			1	1	1
060 Mill Mixing		2	1		
061 Prep. - Reclaim		1	1	1	
062 Devulcanizing - Reclaim	1	1	1		
063 Milling - Reclaim (refining)		1	2		
064 Service - Reclaim		1	1	1	
065 Service - BB - Miscellaneous		1	2		
066 Compounding & Mixing - Chem. Prod.			1	1	1
067 Reaction Operator - Chem. Prod.				2	1
068 Finishing (dry, bag) - Chem. Prod.				2	1
069 Shipping & Receiving - Chem. Prod.				2	1
070 Manufacture Foam Prod.				2	1
071 Rocket Liner Mfg.				2	1
072 Urethane				3	

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
073 Vinyl Prod. Mfg.				3	
074 Resin Prod. Mfg. (chemigum, pliolite, dispersite) 345A split				3	
075 Pliofilm Mixing				3	
076 Pliofilm Fabrication				3	
077 Pliofilm Finishing				3	
078 Batch Prep. - Ind. Prod.	1	1	1		
079 Prep. - Ind. Prod.		2		1	
080 Curing - Ind. Prod.	1	1	1		
081 Finish & Inspect - Ind. Prod.			2	1	
082 Other Rubber Worker - (non-tire & tube)			2	1	
083 Batch Prep. - Hose & Belt	1	1	1		
084 Fabrication - Hose & Belt		2		1	
085 Curing - Hose & Belt	1	1	1		
086 Finish & Inspect - Hose & Belt			1	2	
087 Special Rubber Prod. Development (381A & 357A)			1	2	
088 Other Worker (non-rubber such as police, cafeteria, etc.)				2	
089 Batch Prep. - Synthetic Latex				2	
090 Preparation & Reaction-Synthetic Latex				2	
091 Finishing & Packing-Synthetic Latex				2	
092 Rim Plant - Metal Treatment				3	
093 Rim Plant - Forming & Machining				3	
094 Rim Plant-Welding				3	
095 Rim Plant-Finishing & Inspecting				3	
096 Plastics-Production & Manufacture				3	

INTER-OBSERVER AGREEMENT ON ESTIMATE OF ASBESTOS LEVELS

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
001 Batch Preparation-Tires		1	2		
002 Batch Preparation-Tube, Flaps, Bladders		1	2		
003 Pigment Blending		1	2		
004 Cement Mixing			1	2	
005 Cutting & Milling-Tires		1		2	
006 Cutting & Milling-Tubes	1	1	1		
007 Service-Batch Preparation-Tires	1	1	1		
008 Service-Batch Preparation-Tubes		1	2		
009 Milling-Treads		1	2		
010 Milling-Plystock			2	1	
011 Milling-Flaps & Bladders			2	1	
012 Milling-Tubes			2	1	
013 Milling-Miscellaneous			3		
014 Calender Operation			1	1	
015 Calender Tending				3	
016 Roll Changing-includ. Trucking & Service				3	
017 Plystock Handling-includ. Band Building				3	
018 Liner Service (reroll, mend, clean)				3	
019 Tuber Operation-Treads				3	
020 Tuber Operation-Tubes	1		2		
021 Tuber Operation-Flaps & Bladders			3		
022 Tuber Service-Tubes		1	2		
023 Tuber Service-Flaps & Bladders			3		
024 Tuber Service-Tread Tuber (includ. booking and slitting)				3	

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
025 Cementing-Treads				3	
026 Bead Building				3	
027 Tire Building				3	
028 Service-Tire & Bead Building				3	
029 Inspection, Repair & Sort Green Tires (includ. trucking)				3	
030 Paint & Line-Green Tires			2	1	
031 Valve Preparation			2	1	
032 Tube & Flap Building	2		1		
033 Curing-Tires				3	
034 Curing-Tubes	3				
035 Curing-Flaps (black)			1	2	
036 Curing-Flaps (white)	1		1	1	
037 Curing-Bladders			2	1	
038 Curing-Valves		1		2	
039 Mold Cleaning & Repair				2	
040 Finishing & Inspecting Tires				3	
041 Repairing Tires				3	
042 Finishing & Repairing-Tubes & Airbags		2	1		
043 Finishing & Repairing-Flaps, Bladders and Sleeves			2	1	
044 Maintenance-Painting				2	1
045 Maintenance-Millwright				2	1
046 Maintenance-Electrical			1	1	1
047 Maintenance-Sheet Metal				2	1
048 Maintenance-Welding				2	1

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
049 Mechanic				2	1
050 Carpentry	1			1	1
051 Machinist			1	1	1
052 Maintenance-Misc. (pipefitters, cement finisher, etc.)	1		1		1
053 Power Plant		1		2	
054 Quality Control Testing			1	1	1
055 Trucking (genl.)			1	1	1
056 Clerical				3	
057 Janitor			2		1
058 Shipping & Receiving			1	2	
059 Other Rubber Worker (tires & tubes)			1	1	
060 Mill Mixing	1		2		
061 Prep. - Reclaim				3	
062 Devulcanizing - Reclaim				3	
063 Milling - Reclaim (refining)			1	2	
064 Service - Reclaim			2	1	
065 Service - BB - Miscellaneous			2	1	
066 Compounding & Mixing - Chem. Prod.				2	1
067 Reaction Operator - Chem. Prod.				2	1
068 Finishing (dry, bag) - Chem. Prod.				2	1
069 Shipping & Receiving - Chem. Prod.				2	1
070 Manufacture Foam Prod.				3	
071 Rocket Liner Mfg.				2	1
072 Urethane				3	

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
073 Vinyl Prod. Mfg.				2	1
074 Resin Prod. Mfg. (chemigum, pliolite, dispersite) 345A split				3	
075 Pliofilm Mixing				3	
076 Pliofilm Fabrication				3	
077 Pliofilm Finishing				3	
078 Batch Prep. - Ind. Prod.			2	1	
079 Prep. - Ind. Prod.			2	1	
080 Curing - Ind. Prod.			1	2	
081 Finish & Inspect - Ind. Prod.				3	
082 Other Rubber Worker - (non-tire & tube)				2	1
083 Batch Prep. - Hose & Belt			3		
084 Fabrication - Hose & Belt		1	2		
085 Curing - Hose & Belt				3	
086 Finish & Inspect - Hose & Belt				3	
087 Special Rubber Prod. Development (381A & 357A)				2	1
088 Other Worker (non-rubber such as police, cafeteria, etc.)				3	
089 Batch Prep. - Synthetic Latex				3	
090 Preparation & Reaction-Synthetic Latex				3	
091 Finishing & Packing-Synthetic Latex				3	
092 Rim Plant - Metal Treatment				3	
093 Rim Plant - Forming & Machining				3	
094 Rim Plant-Welding				3	
095 Rim Plant-Finishing & Inspecting				3	
096 Plastics-Production & Manufacture				3	

INTER-OBSERVER AGREEMENT ON ESTIMATE OF NITROSAMINE LEVELS

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
001 Batch Preparation-Tires	1	1	1		
002 Batch Preparation-Tube, Flaps, Bladders	1	1	1		
003 Pigment Blending	3				
004 Cement Mixing				3	
005 Cutting & Milling-Tires		1	1	1	
006 Cutting & Milling-Tubes		1	1	1	
007 Service-Batch Preparation-Tires		1	2		
008 Service-Batch Preparation-Tubes		1	2		
009 Milling-Treads	1	1		1	
010 Milling-Plystock	1	1		1	
011 Milling-Flaps & Bladders	1	1		1	
012 Milling-Tubes	1	1		1	
013 Milling-Miscellaneous	1	1		1	
014 Calender Operation		1	1	1	
015 Calender Tending		1	1	1	
016 Roll Changing-includ. Trucking & Service			1	2	
017 Plystock Handling-includ. Band Building			2	1	
018 Liner Service (reroll, mend, clean)			1	2	
019 Tuber Operation-Treads		1	1	1	
020 Tuber Operation-Tubes		1	1	1	
021 Tuber Operation-Flaps & Bladders		1	1	1	
022 Tuber Service-Tubes			1	2	
023 Tuber Service-Flaps & Bladders			1	2	
024 Tuber Service-Tread Tuber (includ. booking and slitting)			1	2	

OCCUPATIONAL TITLE		High	Med.	Low	None	Unk.
025	Cementing-Treads			1	2	
026	Bead Building			1	2	
027	Tire Building			1	2	
028	Service-Tire & Bead Building				3	
029	Inspection, Repair & Sort Green Tires (includ. trucking)				3	
030	Paint & Line-Green Tires				3	
031	Valve Preparation				3	
032	Tube & Flap Building			1	2	
033	Curing-Tires	1		1	1	
034	Curing-Tubes	1		1	1	
035	Curing-Flaps (black)	1		1	1	
036	Curing-Flaps (white)			2	1	
037	Curing-Bladders		1	1	1	
038	Curing-Valves	1		1	1	
039	Mold Cleaning & Repair	1			2	
040	Finishing & Inspecting Tires			1	2	
041	Repairing Tires		1	2		
042	Finishing & Repairing-Tubes & Airbags			2	1	
043	Finishing & Repairing-Flaps, Bladders and Sleeves			2	1	
044	Maintenance-Painting				2	1
045	Maintenance-Millwright				2	1
046	Maintenance-Electrical			1	1	1
047	Maintenance-Sheet Metal				2	1
048	Maintenance-Welding		1		1	1

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
049 Mechanic				2	1
050 Carpentry				2	1
051 Machinist				2	1
052 Maintenance-Misc. (pipefitters, cement finisher, etc.)				2	1
053 Power Plant				2	1
054 Quality Control Testing			2	1	
055 Trucking (genl.)			1	1	1
056 Clerical				3	
057 Janitor			1	1	1
058 Shipping & Receiving			1	2	
059 Other Rubber Worker (tires & tubes)			1	1	1
060 Mill Mixing	2	1			
061 Prep. - Reclaim			1	2	
062 Devulcanizing - Reclaim		1	1	1	
063 Milling - Reclaim (refining)		1	1	1	
064 Service - Reclaim			1	2	
065 Service - BB - Miscellaneous			3		
066 Compounding & Mixing - Chem. Prod.		2			1
067 Reaction Operator - Chem. Prod.		1		1	1
068 Finishing (dry, bag) - Chem. Prod.	1		1		1
069 Shipping & Receiving - Chem. Prod.			1	1	1
070 Manufacture Foam Prod.	1	1		1	
071 Rocket Liner Mfg.			1	2	
072 Urethane			1	2	

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
073 Vinyl Prod. Mfg.				2	1
074 Resin Prod. Mfg. (chemigum, pliolite, dispersite) 345A split		1		1	1
075 Pliofilm Mixing				2	1
076 Pliofilm Fabrication				2	1
077 Pliofilm Finishing				2	1
078 Batch Prep. - Ind. Prod.	2	1			
079 Prep. - Ind. Prod.		2	1		
080 Curing - Ind. Prod.	1	1		1	
081 Finish & Inspect - Ind. Prod.			2	1	
082 Other Rubber Worker - (non-tire & tube)			1	1	1
083 Batch Prep. - Hose & Belt	2	1			
084 Fabrication - Hose & Belt		1	2		
085 Curing - Hose & Belt	1		1	1	
086 Finish & Inspect - Hose & Belt			2	1	
087 Special Rubber Prod. Development (381A & 357A)		1		2	
088 Other Worker (non-rubber such as police, cafeteria, etc.)				3	
089 Batch Prep. - Synthetic Latex		1		2	
090 Preparation & Reaction-Synthetic Latex		1		2	
091 Finishing & Packing-Synthetic Latex			1	2	
092 Rim Plant - Metal Treatment				3	
093 Rim Plant - Forming & Machining				3	
094 Rim Plant-Welding				3	
095 Rim Plant-Finishing & Inspecting				3	
096 Plastics-Production & Manufacture			1	1	1

INTER-OBSERVER AGREEMENT ON ESTIMATION OF CARBON BLACK LEVELS

OCCUPATIONAL TITLE	High	Med.	Low	None	Uak.
001 Batch Preparation-Tires	3				
002 Batch Preparation-Tube, Flaps, Bladders	3				
003 Pigment Blending	1		2		
004 Cement Mixing				3	
005 Cutting & Milling-Tires	1		1	1	
006 Cutting & Milling-Tubes	1		1	1	
007 Service-Batch Preparation-Tires	1	2			
008 Service-Batch Preparation-Tubes	1	2			
009 Milling-Treads				1	2
010 Milling-Plystock				1	2
011 Milling-Flaps & Bladders				1	2
012 Milling-Tubes				1	2
013 Milling-Miscellaneous				1	2
014 Calender Operation					3
015 Calender Tending					3
016 Roll Changing-includ. Trucking & Service					3
017 Plystock Handling-includ. Band Building					3
018 Liner Service (reroll, mend, clean)					3
019 Tuber Operation-Treads					3
020 Tuber Operation-Tubes					3
021 Tuber Operation-Flaps & Bladders					3
022 Tuber Service-Tubes					3
023 Tuber Service-Flaps & Bladders					3
024 Tuber Service-Tread Tuber (includ. booking and slitting)					3

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
025 Cementing-Treads				3	
026 Bead Building				3	
027 Tire Building				3	
028 Service-Tire & Bead Building				3	
029 Inspection, Repair & Sort Green Tires (includ. trucking)				3	
030 Paint & Line-Green Tires				3	
031 Valve Preparation				3	
032 Tube & Flap Building			1	2	
033 Curing-Tires			1	2	
034 Curing-Tubes			1	2	
035 Curing-Flaps (black)			1	2	
036 Curing-Flaps (white)			1	2	
037 Curing-Bladders			1	2	
038 Curing-Valves			1	2	
039 Mold Cleaning & Repair				3	
040 Finishing & Inspecting Tires		1		2	
041 Repairing Tires		1		2	
042 Finishing & Repairing-Tubes & Airbags		1		1	
043 Finishing & Repairing-Flaps, Bladders and Sleeves		1		2	
044 Maintenance-Painting				2	1
045 Maintenance-Millwright		1		1	1
046 Maintenance-Electrical		1		1	1
047 Maintenance-Sheet Metal	1			1	1
048 Maintenance-Welding		1		1	1

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
049 Mechanic			1	1	1
050 Carpentry				2	1
051 Machinist				2	1
052 Maintenance-Misc. (pipefitters, cement finisher, etc.)		1	1		1
053 Power Plant				3	
054 Quality Control Testing			1	2	
055 Trucking (genl.)			1	1	1
056 Clerical				3	
-057 Janitor		1	1		1
058 Shipping & Receiving			2	1	
059 Other Rubber Worker (tires & tubes)				2	1
060 Mill Mixing		1		1	1
061 Prep. - Reclaim		1		2	
062 Devulcanizing - Reclaim		1		2	
063 Milling - Reclaim (refining)		1		2	
064 Service - Reclaim		1		2	
065 Service - BB - Miscellaneous	1	2			
066 Compounding & Mixing - Chem. Prod.	1			2	
067 Reaction Operator - Chem. Prod.				3	
068 Finishing (dry, bag) - Chem. Prod.				3	
069 Shipping & Receiving - Chem. Prod.				3	
070 Manufacture Foam Prod.				3	
071 Rocket Liner Mfg.				3	
072 Urethane				3	

OCCUPATIONAL TITLE	High	Med.	Low	None	Unk.
073 Vinyl Prod. Mfg.				3	
074 Resin Prod. Mfg. (chemigum, pliolite, dispersite) 345A split				3	
075 Pliofilm Mixing				3	
076 Pliofilm Fabrication				3	
077 Pliofilm Finishing				3	
078 Batch Prep. - Ind. Prod.	2	1			
079 Prep. - Ind. Prod.		1	1	1	
080 Curing - Ind. Prod.		1		2	
081 Finish & Inspect - Ind. Prod.			1	2	
082 Other Rubber Worker - (non-tire & tube)				2	
083 Batch Prep. - Hose & Belt	2	1			
084 Fabrication - Hose & Belt		1	1	1	
085 Curing - Hose & Belt				1	2
086 Finish & Inspect - Hose & Belt				1	2
087 Special Rubber Prod. Development (381A & 357A)			1	1	1
088 Other Worker (non-rubber such as police, cafeteria, etc.)				3	
089 Batch Prep. - Synthetic Latex				3	
090 Preparation & Reaction-Synthetic Latex				3	
091 Finishing & Packing-Synthetic Latex				3	
092 Rim Plant - Metal Treatment				3	
093 Rim Plant - Forming & Machining				3	
094 Rim Plant-Welding				3	
095 Rim Plant-Finishing & Inspecting				3	
096 Plastics-Production & Manufacture				3	

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