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A Retrospective Cohort Mortality Study of Workers Exposed to Formaldehyde in the Garment Industry

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In order to assess the possible human carcinogenecity of formaldehyde we conducted a retrospective cohort mortality study of workers exposed for at least three months to formaldehyde in three garment facilities which produced permanent press garments. A total of 11,030 workers contributing 188,025 person-years were included in the study. Vital status was successfully ascertained through 1982 for over 96% of the cohort. The average (TWA) formaldehyde exposure at the three plants monitored in 1981 and 1984 by NIOSH was 0.15 ppm but past exposures may have been substantially higher. In general, mortality from nonmalignant causes was less than expected. A statistically significant excess in mortality from cancers of the buccal cavity (SMR = 343) and connective tissue (SMR = 364) was observed. Statistically nonsignificant excesses in mortality were observed for cancers of the trachea, bronchus and lung (SMR = 114), pharynx (SMR = 112), bladder (SMR = 145), leukemia and aleukemia (SMR = 113), and other lymphopoietic neoplasms (SMR = 170). Mortality from cancers of the trachea, bronchus and lung was inversely related to duration of exposure and latency. In contrast, mortality from cancers of the buccal cavity, leukemias, and other lymphopoietic neoplasms increased with duration of formaldehyde exposure and/or latency. These neoplasms also were found to be highest among workers first exposed during a time period of high potential formaldehyde exposures in this industry (1955–1962). However, it should be recognized that these findings are based on realtively small numbers and that confounding by other factors may still exist. The results from this investigation, although far from conclusive, do provide evidence of a possible relationship between formaldehyde exposure and the development of upper respiratory cancers (buccal), leukemias, and other lymphopoietic neoplasms in humans.

Key words: respiratory neoplasms, occupational diseases

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INTRODUCTION

An estimated 1.6 million Americans are potentially exposed to formaldehyde in the workplace [NIOSH, 1981] and over 100 million Americans are exposed to low levels (.03–.25 ppm) of formaldehyde in their homes [EPA, 1985]. Concern over the possible human carcinogenecity of formaldehyde is based primarily on the findings of an excess of nasal squamous cell carcinomas in two independent studies of rodents exposed to formaldehyde via inhalation [Albert et al., 1982; Swenberg et al., 1980].

The findings from several previous epidemiologic studies of workers exposed to formaldehyde have been reported [Acheson et al., 1984; Harrington and Shannon, 1975; Harrington and Oakes; 1984, Levine et al., 1984; Liebling et al., 1983; Marsh, 1982; Walrath and Fraumeni, 1983; Walrath and Fraumeni, 1984; Blair et al., 1986; and Stroup, 1984]. None of these investigations has detected an excess of nasal cancer, although the statistical power of these studies to detect this rare form of cancer was extremely low. An association between occupational formaldehyde exposure and nasal cancer has recently been reported in two case-control studies [Hayes et al., 1986; Olsen, 1984]. Recently, Vaughn et al. (1986) reported the results from a population based nasal cancer case-control study in which a strong association was observed between residential formaldehyde exposure and nasal cancer, and only a weak association between occupational formaldehyde exposure and nasal cancer.

Other cancer sites have been reported to be in excess in studies of workers exposed to formaldehyde. An excess of lung cancer was reported in two studies of industrial workers [Acheson et al., 1984; Blair et al., 1986]. Buccal-pharyngeal cancers were reported to be in excess in one study of chemical workers exposed to formaldehyde; however, this excess was only based on two cases. Recently, Blair et al. [1983] reported an excess of nasopharyngeal and oropharyngeal cancers in industrial workers exposed to formaldehyde. Finally, brain cancers and lymphopoietic neoplasms have been observed to be in excess in studies of pathologists [Harrington and Shannon 1975; Harrington and Oakes 1984], anatomists [Stroup, 1984] and embalmers [Levine et al., 1984; Walrath and Fraumeni, 1983; Walrath and Fraumeni, 1984], but not in excess in studies of industrial workers [Acheson, 1984; Marsh, 1982; Wong, 1983; Blair, 1986].

In a previous paper [Stayner et al., 1985], we reported the findings of a proportionate mortality (PMR) study of workers in three garment plants exposed to formaldehyde. Statistically significant ($p<.05$) elevations in mortality were observed for malignant neoplasms of the buccal cavity, biliary passages and liver, and other lymphatic and hematopoietic sites. Following are the results of a retrospective cohort mortality study which we conducted in three garment plants (two of which were included in the previous PMR study) in order to further evaluate the possible relationship between cancer risk and formaldehyde exposure.

METHODS

Workers were selected for inclusion in this study from three garment manufacturing facilities, which will be referred to as plants 1, 2, and 3. Plants 1 and 3 are located in Georgia, and plant 2 is located in Pennsylvania. These garment facilities produce shirts from fabrics which are treated with formaldehyde resins in order to

impart crease resistance and other desirable properties. The fabrics emit unreacted formaldehyde gas resulting in potential occupational exposures.

Company personnel records were copied for workers employed at the three facilities. A computer file was created containing demographic and work history information. Workers included in the study cohort must have worked for at least three months between the time when formaldehyde fabrics were first introduced into the production process and December 31, 1977. The use of formaldehyde treated fabrics began in 1959 at plants 1 and 2, and in 1955 at plant 3. Workers who were employed only in clerical or administrative positions were excluded.

Union records were copied at facilities 1 and 2 as an auxiliary source of information and for verification of the completeness of the personnel files. Internal Revenue Service (IRS) quarterly earnings reports obtained for plant 3 were used for verification of the completeness of this plant's personnel files.

The vital status of the cohort members was ascertained through the use of the following information sources: the Social Security Administration, Internal Revenue Service, local post offices, state motor vehicle departments, and the National Death Index. Through these sources, the vital status of the workers was traced up to December 31, 1982. Death certificates were obtained for deceased individuals from state vital statistics bureaus, and the cause of death was coded by a nosologist using the International Classification of Disease (ICD) codes in effect at the time of death.

A modified life-table analysis was performed using a program [Waxweiler et al., 1983], which computes expected numbers of deaths by multiplying cause, 5 year age, 5 year calendar-time, race and sex specific mortality rates from the U.S. population by the corresponding person-years distribution from the study population. At the time of this study, our life-table analysis system only maintained U.S. mortality rates through 1978. In order to calculate expected deaths through 1982, the death rates for the interval 1975–78 were used for the period 1979–82. Similarly, state rates also were used to compute expected numbers of deaths. Standardized mortality ratios (SMRs) were calculated by dividing the number of observed deaths by the number expected and multiplying by 100. Thus, an SMR which exceeds 100 indicates that the observed number of deaths exceeds the number expected based upon the experience of the comparison population. The results from the life-table analysis were stratified by time since first exposure (latency), plant site, sex and race groups, year of first exposure, and duration of exposure. For the duration of exposure analysis, the mortality experience of the cohort was divided into three groups so that each group had an approximately equal number of expected cancer deaths. This approach was used to insure that each of the groups had approximately equal statistical power for detecting a cancer excess. The analysis by latency was divided into three 10 year groups, based on the a priori assumption that cancers related to formaldehyde exposure would be unlikely to develop among workers with less than 10 years of latency, and that some cancers (i.e., solid tumors) might require 20 years of latency.

Exact ninety-percent confidence intervals and p values were computed based on the assumption of a Poisson distribution. SMRs were considered to be statistically significant if the p value was less than 0.05 (one-tail) or equivalently if the lower confidence limit was greater than 100.

Extensive industrial hygiene monitoring for formaldehyde was performed at the three study facilities by NIOSH since 1981. Formaldehyde exposure levels were

determined for 549 of 1373 (40%) current employees within five different departments across the three facilities. The number of employees randomly selected within each department for exposure sampling was based on the number of individuals in that department and reflects a 95% confidence level (power) at an alpha = .05 level that the highest and lowest exposed individuals were included in the sampling. Personal exposures to formaldehyde were measured using a NIOSH sampling method (P&CAM #354) [NIOSH, 1981]. Continuous air monitoring for formaldehyde also was conducted throughout various areas of each plant to determine ambient and peak (emission source) formaldehyde concentration levels. Information on historic exposure levels to formaldehyde were not available for these facilities.

Potential confounding exposures were also evaluated in each plant. Sampling for phenol, organic cleaning solvents, and nuisance dust was conducted. No other possible confounding exposures were identified in these plants.

FINDINGS

A total of 11,030 workers contributing 188,025 person-years were included in this study. The distribution of the cohort by vital-status, sex, race, plant site, duration of employment, latency, and first year of exposure is presented in Table I. The vital status was successfully ascertained through 1982 for over 96% of the cohort. The remaining 4% of the cohort were lost to follow-up and were assumed to be alive in this analysis until the end of the study time period (12/31/82). Death certificates were obtained for all but 22 (3.6%) of the 609 deaths observed in this study. Deaths with missing death certificates were included in the 'Other & Unknown Causes' category. The study population is primarily white (75.6%) and female (81.8%). Approximately 50% of the workers and person-years are from plant 1. The duration of exposure and latency of the cohort is relatively short with a median of 3.2 and 15.8 yr, respectively. About half of the workers (42%) and person-years (57%) were first exposed to formaldehyde prior to 1963. The cohort is predominantly middle aged with a median year of birth of 1938.

Comparison of the company's personnel records with union records (plant 1 and 2), or IRS records (plant 3) revealed that the records from plants 1, 2, and 3 were respectively 85.9, 96.4, and 96.8 percent complete. Workers from plants 1 and 2, who were missing company personnel records were added to the cohort using information contained in the union records. Union records were not available for plant 3. Thus, overall this cohort is believed to be close to 100% complete, for plants 1 and 2, and 97% complete for plant 3.

A summary of recent formaldehyde exposure levels by department for each plant since is presented in Table II. The overall range of the geometric mean (GM) exposure is narrow (0.14–0.17 ppm, GM = 0.15). These results depict the potential for recent formaldehyde exposure in these garment facilities to be homogeneous within and across plants, and to be low (GM = 0.15 ppm). Continuous area monitoring revealed that formaldehyde levels were relatively constant (i.e., no substantial peak levels or intermittent exposures) over the workshift. Formaldehyde exposures are believed to have been substantially higher in the past (see Discussion section).

The industrial hygiene surveys did not identify any other chemical exposures at these facilities which could result in substantial confounding of the study findings.

TABLE I. Vital Status, Demographic and Work Characteristics of the Study Population

Variable	Persons		Person-Years	
	Number	Percent	Number	Percent
Vital status				
Alive	10,031	90.9	—	—
Deceased	609	5.5	—	—
Unknown	390	3.5	—	—
Sex/race				
White male	1,602	14.5	26,064	13.9
Nonwhite male	406	3.7	4,891	2.6
White female	6,741	61.1	131,160	69.8
Nonwhite female	2,281	20.7	25,910	13.8
Plant Site				
Plant 1	5,688	51.6	92,508	49.2
Plant 2	1,852	16.8	33,656	17.9
Plant 3	3,490	31.6	61,860	32.9
Duration of employment				
3 months to 4 yr	5,967	54.1	109,048	58.0
4 yr to 10 yr	2,482	22.5	48,382	25.7
10 yr +	2,581	23.4	30,596	16.3
Latency				
3 months to 10 yr	2,989	27.1	103,233	54.9
10 to 20 yr	4,324	39.2	68,170	36.3
20 yr +	3,717	33.7	16,622	8.8
First year exposed				
Prior to 1963	4,674	42.3	106,578	56.7
1963 up to 1971	3,792	34.4	59,331	31.6
1971 up to 1978	2,564	23.2	22,117	11.8

TABLE II. Current Formaldehyde Exposure Levels (ppm) by Department and Plant*

Department	Plant 1			Plant 2			Plant 3[b]			Combined total		
	N	GM	GSD	N	GM	GSD	N	GM	GSD	N	GM	GSD
Cutting[a]	12	0.20	1.21	29	0.09	2.67	0	—	—	41	0.14	1.84
Collar	33	0.20	1.26	27	0.09	2.19	30	0.14	1.55	90	0.16	1.43
Parts	30	0.17	1.54	46	0.18	2.06	37	0.14	1.70	113	0.17	1.67
Assembly	73	0.09	2.32	66	0.19	2.08	73	0.18	2.28	212	0.15	2.21
Packaging[a]	45	0.11	2.03	20	0.15	2.14	28	0.14	2.85	93	0.14	2.03
										549	0.15	1.90

*Abbreviations used in this table indicate the following: ppm = parts per million; N = number of employees sampled; GM = geometric mean exposure level; GSD = geometric standard deviation.
[a]Plant 1 was surveyed during 1981 and plants 2 and 3 were surveyed in 1984.
[b]Plant 3 did not have a cutting department.

Measurements for phenol were nondetectable. Organic vapor exposures ranged from non-detectable to 5.0 ppm for methychloroform and non-detectable to 1.0 ppm for 1,1,2 trichloroethane. These exposures were significantly lower than the most stringent exposure standards and involved only one or two exposed workers in each plant. Nuisance dust levels were minimal (nondetectable to 1.5 mg/m^3).

The results from the life-table analysis for all causes of death are presented in Table III. Mortality from all causes (SMR = 74) was less than expected. This is consistent with other studies of industrial cohorts in which overall mortality and

TABLE III. Results From the Life-Table Analysis for all Causes of Death*

Cause of death[b]	OBS	EXP	SMR	90% CI	
				Lower	Upper
All malignancies (MN)	186	226.1	82	73	93
MN buccal cavity and pharynx	6	3.9	155	68	307
MN buccal cavity	4	1.2	343[a]	118	786
MN pharynx	2	1.8	113	20	359
MN digestive organs and peritoneum	30	51.5	58	42	79
MN esophagus	2	2.6	77	14	243
MN stomach	4	6.6	60	21	138
MN intestine	15	21.9	68	42	106
MN biliary passages and liver	2	3.8	52	9	166
MN pancreas	5	9.5	52	21	111
MN respiratory system	39	36.8	109	82	142
MN trachea bronchus and lung	39	34.1	114	86	149
MN breast	33	47.5	69	51	93
MN genital organs	25	34.5	73	50	101
MN urinary organs	5	6.2	80	32	169
MN kidney	2	3.5	55	10	178
MN bladder and other	3	2.7	112	31	290
MN lymphopoietic neoplasms	18	19.8	91	59	135
Lymphosarcoma and reticulosarcoma	4	6.4	62	21	142
Leukemia and aleukemia	9	7.9	114	60	200
Other lymphopoietic neoplasms	5	2.9	170	67	357
MN skin	2	3.8	52	9	166
MN brain and other nervous tissue	5	7.0	71	28	149
MN connective tissue	4	1.1	364[a]	123	825
MN other and unspecified sites	19	15.2	125	82	184
Diabetes mellitus	4	17.8	22	8	51
Diseases nervous system	44	64.5	68	52	88
Diseases Circulatory System	188	260.3	71	63	81
Diseases respiratory system	26	36.0	71	51	100
Pneumonia	9	16.4	54	29	96
Bronchitis	4	2.1	190	65	435
Other respiratory diseases	13	15.9	81	48	130
Diseases digestive system	19	33.2	57	38	84
Cirrhosis of the liver	18	25.7	70	45	104
Diseases genito-urinary system	6	9.6	62	27	124
Accidents and violence	78	97.6	80	66	96
Other and unknown causes	49	47.2	103	81	132
All causes	609	822.0	74	69	79

*Abbreviations used in this table indicate the following: OBS = observed number of deaths; EXP = expected number of deaths; 90 % CI = ninety percent confidence interval; SMR = standardized mortality ratio.

[a]Significant at the $p < .05$ level.

[b]Death categories with only one death are not reported in this Table. Results are for all race/sex groups combined.

mortality from nonmalignant causes is often depressed due to the "healthy worker effect" [McMichael, 1976]. Mortality from nonmalignant causes was generally less than expected, with the exception of a statistically nonsignificant excess of bronchitis (SMR = 190). Mortality for all malignant neoplasms was also less than expected (SMR = 82). However, certain specific malignant death categories were observed to

TABLE IV. Results From the Life-Table Analysis Stratified by Sex and Race Groups for Selected Malignant Causes of Death*

	W male		W female		NW male		NW female	
Cause of death	OBS	SMR	OBS	SMR	OBS	SMR	OBS	SMR
MN buccal cavity	0	—	4	485[a]	0	—	0	—
MN pharynx	1	239	1	86	0	—	0	—
MN trachea, bronchus and lung	14	133	22	97	1	85	2	190
MN bladder	0	—	3	169	0	—	0	—
MN connective tissue	1	630	3	235	0	—	0	—
Leukemia and aleukemia	0	—	9	152	0	—	0	—
Other lymphopoietic	0	—	4	172	0	—	1	611

*Abbreviations used in this table indicate the following: OBS-observed number of deaths; MN-malignancy; SMR-standardized mortality ratio.
[a]Significant at the $p < .05$ level.

TABLE V. Results Stratified by Plant Location for Selected Malignant Causes of Death Using the U.S. Rates (SMR) and State Rates (SSMR) as the Comparison*

	Plant 1			Plant 2			Plant 3		
Cause of death	OBS	SMR	SSMR	OBS	SMR	SSMR	OBS	SMR	SSMR
MN buccal cavity and Pharynx	3	137	127	2	270	317	1	106	91
MN buccal cavity[b]	2	306	—	2	886[a]	—	0	—	—
MN pharynx[b]	1	100	—	0	—	-	1	234	—
MN trachea, bronchus and lung	29	149[a]	155[a]	5	74	78	5	61	59
MN bladder	1	66	75	1	199	183	1	152	156
MN connective tissue[b]	3	514[a]	—	0	—	—	1	318	—
Leukemia and aleukemia	4	96	97	1	65	64	4	178	177
Other lymphopoietic[b]	3	186	—	1	171	—	1	130	—

*Abbreviations used in this table indicate the following: OBS-observed number of deaths; MN-malignancy; SMR-standardized mortality ratio, SSMR-SMR using state rates.
[a]Significant at the $p < .05$ level.
[b]State rates were not available for cancers of the buccal cavity, pharynx, connective tissue, and other lymphopoietic neoplasms. Results for all race/sex groups combined.

be in excess. Mortality from cancer of the buccal cavity (SMR = 343, CI = 118,786) and connective tissue (SMR = 364, CI = 123,825) was elevated at a statistically significant level. Statistically nonsignificant excesses in mortality were observed for the following malignant death categories: trachea, bronchus and lung (SMR = 114), pharynx (SMR = 113), bladder (SMR = 112), leukemia and aleukemia (SMR = 114), and other lymphopoietic neoplasms (SMR = 170). Presentation of the following stratified analyses will be limited to results for the cancer sites found to be in excess in the overall analysis (Table III).

Race and sex specific analyses for the selected cancer sites are presented in Table IV. Among white females, the largest sex-race group in the study, a significant excess of buccal cavity cancer (SMR = 485), and a nonsignificant excess of cancers of the bladder (SMR = 169), connective tissue (SMR = 235), leukemias (SMR = 152) and other lymphopoietic neoplasms (SMR = 172) were observed. A nonsignificant

TABLE VI. Results Stratified by Duration of Employment and Latency Period for Selected Neoplasms*

Cause of death[c]	Latency period	Duration of exposure: 3M—3Y OBS	3M—3Y SMR	4Y—9Y OBS	4Y—9Y SMR	10Y + OBS	10Y + SMR	Overall OBS	Overall SMR
MN buccal cavity	3M—9Y	0	—	0	—	0	—	0	—
	10Y—19Y	0	—	0	—	2	822[a]	2	357
	20Y +	0	—	1	1315	1	654	2	705[a]
	TOTAL	0	—	1	276	3	757[b]	4	343[a]
MN pharynx	3M—9Y	0	—	0	—	0	—	0	—
	10Y—19Y	1	368	1	490	0	—	2	233
	20Y +	0	—	0	—	0	—	0	—
	OVERALL	1	157	1	193	0	—	2	113
MN trachea, bronchus and lung	3M—9Y	7	165	6	180	0	—	13	171[a]
	10Y—19Y	9	159	3	70	6	80	18	103
	20Y +	2	111	2	219	4	79	8	87
	OVERALL	18	154	11	111	10	80	39	114
MN bladder	3M—9Y	0	—	0	—	0	—	0	—
	10Y—19Y	0	—	0	—	1	200	1	79
	20Y +	1	670	0	—	1	255	2	255
	OVERALL	1	116	0	—	2	224	3	112
MN connective tissue	3M—9Y	1	401	0	—	0	—	1	256
	10Y—19Y	1	569	1	826	0	—	2	400
	20Y +	0	—	1	1736	0	—	1	461
	OVERALL	2	426	2	619[a]	0	—	4	364[a]
MN leukemia	3M—9Y	1	54	1	95	0	—	2	69
	10Y—19Y	0	—	1	112	1	75	2	59
	20Y +	3	926[a]	0	—	2	243	5	310[a]
	OVERALL	4	120	2	83	3	140	9	114
Other lymphopoietic	3M—9Y	1	250	0	—	0	—	1	134
	10Y—19Y	0	—	0	—	3	498[a]	3	218
	20Y +	0	—	0	—	1	224	1	121
	OVERALL	1	105	0	—	4	381[a]	5	170

*The following abbreviations were used in this table: OBS-observed, SMR-standardized mortality ratio, M-months, Y-years.
[a]Significant at the $p < .05$ level.
[b]Significant at the $p < .01$ level.
[c]Results for all race/sex groups combined.

excess of cancers of the trachea, bronchus, and lung was observed among white males (SMR = 133) and nonwhite females (SMR = 190).

Plant specific analyses for the selected cancer sites are presented in Table V. Significant excesses in mortality were observed for cancers of the buccal cavity in plant 2 (SMR = 886), and cancers of the connective tissues (SMR = 514) and trachea, bronchus, and lung (SMR = 149) in plant 1. Nonsignificant excesses in mortality were observed for cancers of the buccal cavity (SMR = 306), and other lymphopoietic neoplasms (SMR = 186) in plant 1, and for leukemia in plant 3 (SMR = 178). In order to evaluate whether regional variations in mortality rates could explain these findings, plant specific analyses were conducted using state rates as the comparison population (Table V) for the causes of death for which comparable state rates were available. The results from the U.S. and state analyses were generally in close agreement.

TABLE VII. Results Stratified by Year of First Exposure for Selected Malignant Causes*

	Year of first exposure					
	1955–1962		1963–1970		1971–1978	
Cause of death[a]	OBS	SMR	OBS	SMR	OBS	SMR
MN buccal cavity	4	440[b]	0	—	0	—
MN pharynx	1	76	1	273	0	—
MN trachea, bronchus and lung	25	96	10	146	4	295[b]
MN bladder	3	135	0	—	0	—
MN connective tissue	2	248	2	832[b]	0	—
Leukemia and aleukemia	9	154	0	—	0	—
Other lymphopoietic	4	164	0	—	1	1,000

*Abbreviations used in this table indicate the following: OBS-observed number of deaths; MN-malignancy; SMR-standardized mortality ratio.
[a]SMRs were not calculated for categories with only one death. Results for all race/sex groups combined.
[b]Significant at the $p < .05$ level.

The results from stratified analyses by duration of exposure and latency are presented in Table VI. With the exception of cancers of the trachea, bronchus and lung, all of the cancer sites were in greatest excess among workers with more than 10 yr of latency. Cancers of the buccal cavity (SMR = 705) and leukemia (SMR = 310) were significantly elevated among workers with 20 or more yr of latency. Cancers of the trachea, bronchus, and lung (SMR = 171) were significantly elevated among workers with less than 10 yr of followup.

Mortality from cancers of the buccal cavity (SMR = 757), and other lymphopoietic neoplasms (SMR = 381) was significantly elevated among workers in the longest duration of exposure group (10 or more yr). Mortality from leukemia (SMR = 140) and bladder cancer (SMR = 224) was highest in the longest duration of exposure group. Leukemia mortality also was elevated in the shortest duration of exposure group (SMR = 120). Mortality from cancers of the trachea, bronchus and lung appeared to be inversely related to duration of exposure. Mortality from cancer of the connective tissues was significantly elevated among workers with moderate (4 to 9 yr) duration of exposure (SMR = 619).

Finally, the results from analyses stratified by year of first exposure are presented in Table VII. Mortality from cancers of the trachea, bronchus and lung (SMR = 284) was highest among workers first exposed after 1971. Mortality from cancers of the buccal cavity (SMR = 440), bladder (SMR = 135), leukemia (SMR = 154), and other lymphopoietic neoplasms (SMR = 164) was highest among workers employed during the earliest time period (1955 to 1962). Mortality from cancers of the connective tissues (SMR = 1195) was significantly elevated among workers employed during the middle time period (1963–1970).

DISCUSSION

In contrast to the findings from animal studies [Swenberg et al., 1980; Albert et al., 1982], no cases of nasal cancer were observed in this study. This may result from the limited statistical power of this study to detect nasal cancer or the lack of an

association between formaldehyde exposure and nasal cancer in humans. Recently, two case-control studies of nasal cancer have reported an estimated relative risk for occupational exposure to formaldehyde of between 1.6 (Olsen et al., 1984) and 2.5 (Hayes et al., 1986). Using the higher estimate of relative risk (2.5), it is estimated that the current study would only have a 20% chance (power) to detect an excess of this magnitude or greater (alpha = .05).

A nonsignificant excess in mortality from cancers of the trachea, bronchus and lung was observed in this study. This excess, however, was highest among white male workers with short durations of exposure and latency. Mortality from respiratory cancer was significantly elevated at plant 1, but was highest among workers with brief exposures and latency periods at this location. Lung cancer mortality was also highest among workers who were first exposed during recent years when the intensity of formaldehyde exposures was the lowest. This pattern is inconsistent with the hypothesis that the excess in respiratory cancer mortality is related to formaldehyde exposure, since the effects of occupational carcinogens generally do not appear prior to a long latency period (at least 10 yr) and are generally dose related. The power of this study to detect a two–fold excess of lung cancer in workers with at least 20 yr of latency and 10 yr of exposure is 58%.

Lung cancer was only observed to be in excess in plant 1. This might argue against this excess being related to formaldehyde. It should be recognized that plant 1 was the largest facility and that the statistical power was limited for the other plants. Among workers with at least 20 yr of latency and 10 yr of exposure, the statistical power to detect a SMR of 200 for lung cancer was only 21% for plant 2 and 32% for plant 3. The lack of consistency between facilities for the other less common cancer sites may also be a result of limited statistical power.

We observed a statistically significant excess in mortality from cancers of the connective tissue, and a nonsignificant excess in bladder cancer. Excess mortality from these sites have not been observed to be elevated in the animal studies (Swenberg et al., 1980; Albert et al., 1982), or in any of the previously reported epidemiologic studies of formaldehyde exposed workers.

Among the most noteworthy findings in this study was a statistically significant excess of cancers of the buccal cavity. Unlike rats which are obligate nose breathers, humans may breathe either through the nose or mouth. Thus, the oral cavity was considered a priori to be a biologically plausible site for cancer induction by formaldehyde in humans. Two of the four buccal cavity cancer cases were parotid tumors, and the other two cases were cancers of the oral mucosa and soft palate. Hospital pathology reports could only be obtained for two of the cases which were both described as squamous cell carcinomas (one parotid gland duct and one oral mucosa), a histology consistent with that reported in animal studies [Swenberg et al., 1980; Albert et al., 1982]. The other two cases were described on their death certificates as an adenocarcinoma of the parotid and as a carcinoma of the soft palate. Given the rapid metabolism of formaldehyde to formic acid [Heck, 1982], it is somewhat speculative as to what extent formaldehyde would reach the parotid glands which are internal to the oral cavity. One of the parotid gland tumors, however, was a cancer of the salivary gland duct which would have potential for direct contact with formaldehyde. The two pharyngeal cancers observed in this study were both squamous cell carcinomas of the tonsils.

While mortality from pharyngeal cancer was only slightly elevated in this study,

cancers of the tonsils only comprise approximately 16% of the pharyngeal cancer ICD category [NCHS, 1981]. Using this proportion, it is estimated that only 0.29 cases of cancers of the tonsil were expected, resulting in a significant SMR of 694 (CI = 123, 2187). The lack of an excess in buccal cavity cancer in plant 3 may suggest that buccal cavity cancer is unrelated to formaldehyde, or may be a reflection of the fact that due to the small numbers of deaths expected (0.3), the probability (power) of detecting an excess of buccal cavity cancer at this plant was quite low.

There is limited evidence to suggest a possible relationship between formaldehyde exposures and the development of buccal-pharyngeal cancers in humans. Liebling et al. [1983] reported a significant excess of buccal-pharyngeal cancers (PMR = 870) among a cohort of chemical workers exposed to formaldehyde, based on only two observed cases. Walrath and Fraumeni [1983] observed a twofold excess of buccal-pharyngeal cancer among individuals who were licensed as embalmers in New York State. Their study did not observe an excess of buccal-pharyngeal cancers among individuals who were also liscensed as funeral directors; however, according to this report, funeral directors have a lower potential for exposure to formaldehyde than individuals licensed only as embalmers. Recently, Blair et al. [1986] reported a statistically significant excess of nasopharyngeal cancer (SMR = 300) and a statistically nonsignificant excess of oropharyngeal (SMR = 192) cancer among industrial workers exposed to formaldehyde. Other studies of formaldehyde exposed workers have not reported an excess of buccal-pharyngeal cancers [Acheson et al., 1984; Harrington and Shannon, 1975; Wong, 1983].

Leukemias and other lymphopoietic neoplasms were also considered a priori to be a possible site for a formaldehyde effect. Such an effect is inconsistent with the findings from animal studies but consistent with several epidemiologic studies. An excess in mortality from leukemia has consistently been reported in studies of embalmers [Levine et al., 1984, Walrath and Fraumeni, 1983, 1984]. An excess of leukemia (SMR = 148), particularly myelogenous leukemias, was also reported by Stroup [1984] in a study of anatomists. Thirty-eight percent (3 out of 8) of the leukemia cases in our study were of the myeloid type, as compared with the percentage (47%) of myeloid leukemia deaths in the U.S. population [NCHS, 1981]. Finally, Harrington and Shannon [1975] reported a statistically significant excess of lymphoma and hematopoietic neoplasms (SMR = 242) among male British pathologists. In this study, four of the five cases (80%) in the "other lymphopoietic neoplasms" category were multiple myelomas, and the fifth was a poorly differentiated lymphoma. Among U.S. adults, approximately 57% of the deaths in this category are multiple myelomas [NCHS, 1981]. In contrast to the consistent findings in studies of professional groups, epidemiologic studies of industrial groups have failed to detect an excess of leukemia or other lymphopoietic neoplasms [Acheson et al., 1984; Marsh, 1982; Blair et al., 1986]. Other chemical or biologic exposures common to embalmers and pathologists but absent from the industrial cohorts studied may explain the inconsistent findings for these groups. Thus, our study represents the only study of an industrial cohort in which an excess of leukemias and other lymphopoietic neoplasms has been reported.

Studies of pathologists, anatomists and embalmers have reported an excess of brain cancer [Harring and Oakes, 1984; Levine et al., 1984; Walrath and Fraumeni, 1983, 1984; Stroup, 1984]. However, in the study by Harrington and Shannon, this excess occurred primarily among pathologists specializing in hematology and

bacteriology, who may have less exposure to formaldehyde than other pathologists. Mortality from brain cancer was less than expected in our study. Other studies of industrial groups exposed to formaldehyde have also not demonstrated an excess of brain cancer [Acheson et al., 1984; Blair et al., 1986; Marsh, 1982; Wong 1983]. It may be that exposure to chemicals other than formaldehyde or to other biologic agents to which both medical and funeral professionals are exposed may explain these findings. This study only had an 18% chance (power) to detect a SMR of 200 among workers with 20 yr of latency and 10 yr of exposure.

In this study, excess mortality for buccal cancer, leukemias and other lymphopoietic neoplasms was observed to be highest among workers with long duration of formaldehyde exposures, and/or adequate latency periods (10 or more yr). Such a pattern is consistent with an occupational etiology. This interpretation is further supported by the observation that mortality for these sites was highest among workers who were first exposed during the early years of this study when the intensity of formaldehyde exposures was the highest.

A previous proportionate mortality (PMR) study of garment workers, (Stayner et al., 1985) reported an excess of buccal cavity cancer (PMR = 750), other lymphopoietic neoplasms (PMR = 400), and cancers of the biliary passages and liver (PMR = 313). Those results are consistent with this study except for mortality from cancers of the biliary passages and liver, which was less than expected in this study. Two of the facilities in this investigation (plants 1 and 2) were also included in our earlier PMR study; the third plant in this study was not included in the previous (PMR) study. The populations in these two studies also differ in that the PMR study primarily included workers with long durations of exposure, whereas, this study includes a substantial number of workers with short exposures. Two of the buccal cavity cancer cases observed in this study were also included in the previous PMR study. Three cases of the other lymphopoietic neoplasms (2 multiple myelomas and 1 lymphoma) observed in this study were also included in the previous study; the other two cases (2 multiple myelomas) were unique to this study.

Although recent formaldehyde exposures were found to be quite low (GM = 0.15 ppm) in these facilities, past exposures are believed to have been substantially higher since the resin systems used in treating permanent press fabrics have been continually improved to reduce the amount of free formaldehyde in the fabrics. In 1966, Blejer and Miller [1966] reported 0.9 to 2.7 ppm formaldehyde air levels in a garment manufacturing plant. Also in 1966, Shipkovitz [1966] reported short-term (10 min) personal exposure samples of 0.30 to 2.7 ppm of formaldehyde in eight garment plants. In the 1973 Ahmad and Whitson report from a garment plant in which workers were demonstrating symptoms of severe formaldehyde exposures, formaldehyde concentrations ranged between 2 and 10 ppm. Finally, Goldstein [1973] estimated that formaldehyde concentrations in the cutting rooms of garment plants were reduced from approximately 10 ppm in 1968 to less than 2 ppm by 1973 as the result of improved resin treating processes. Despite the reports by Goldstein, Ahmad and Whitson, it is difficult to imagine workers tolerating formaldehyde exposures as high as 10 ppm. In summary, this information indicates that formaldehyde exposures were historically higher and have been effectively reduced through the use of improved formaldehyde resin formulations.

Although our surveys did not uncover any other substantial confounding exposures at these facilities, it is impossible to rule out the possibility that other

non-occupational factors could confound the study findings. The fact that the results were not appreciably altered by the use of state rates suggests that local mortality patterns are an unlikely explanation for these findings. Cancer of the buccal cavity has been associated with alcohol usage [Schottenfeld and Fraumeni, 1982] and with cigarette, pipe and cigar smoking [HEW, 1979]. In addition, snuff dipping, particularly among women in the South, has been shown to be strongly associated with oral cancer risk [Winn, et al. 1981]. Two of the 4 observed cases of buccal cavity cancer were from one of the Southern plants (plant 1) included in this study. These cases were cancers of the soft palate and oral mucosa. The results from our study provide indirect evidence that alcohol and cigarette consumption is an unlikely explanation for the observed excess of buccal cavity cancer. The fact that mortality from cirrhosis of the liver was less than expected (SMR = 70) suggests that alcohol consumption in this population was actually less than in the U.S. population. The excess in mortality from buccal cavity cancer was among white females and was unlikely to be due to smoking since this group did not demonstrate an excess of lung cancer, esophageal cancer, cardiovascular disease, or nonmalignant respiratory disease other than bronchitis. Also among the sample of current workers included in our industrial hygiene surveys, the overall prevalence of cigarette smokers was 29.4%. In plant 1 the prevalence was 26.6%, in plant 2 it was 33.5%, and in plant 3 it was 29.4%. These figures are similar to those reported in a 1980 survey of adult Americans, in which 29.2% of females and 38.3% of males over the age of 20 were current cigarette smokers [NCHS, 1985].

The next-of-kin of the individuals who died from buccal cavity cancer in this study were interviewed in order to obtain more direct information on the possible influence of tobacco and alcohol usage on the study findings. All four cases were described as using alcohol infrequently. One of the cases (oral mucosa cancer) was reported to have dipped snuff and another (soft palate cancer) was reported to have been a moderate cigarette smoker (less than 1/2 pack per day). The other 2 cases were reported not to have used any form of tobacco.

In conclusion, the positive and negative findings of this investigation must be interpreted cautiously. Although no cases of nasal cancer were observed, this study lacked sufficient statistical power to detect a significant excess of this rare cancer. In addition, the latency of the cohort may be too short if nasal cancer has a long latency period. A statistically nonsignificant excess in mortality from cancers of the trachea, bronchus and lung was observed. However, this excess was highest among workers with both short durations of exposure and latency and is thus thought to be unrelated to formaldehyde exposure at these facilities. To fully understand the apparent excess of lung cancer would require more detailed information about cigarette smoking habits, and exposure of these individuals to formaldehyde or other possible pulmonary carcinogens from previous employment in other plants. Mortality from buccal cavity cancer, leukemias, and other lymphopoietic neoplasms was observed to be in excess. Mortality for these sites was highest among workers with adequate latency periods, long durations of exposure, and among workers who were first employed during a period of potentially high formaldehyde exposures in this industry. These facts are consistent with the hypothesis that these positive findings are related to formaldehyde. These findings, however, are not entirely consistent with studies in animals or with other epidemiologic studies of formaldehyde exposed workers. Furthermore, it should be recognized that these findings are based upon a relatively

small number of cases, and that confounding factors may still exist. The authors believe that the results from this investigation, although far from conclusive, do provide evidence of a possible relationship between formaldehyde exposure and the development of upper respiratory cancers (buccal), leukemias and other lymphopoietic neoplasms in humans.

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REFERENCES

Acheson ED, Barnes HR, Gardner MJ, Pannett B, Barnes HR, Osmond C, Taylor CP (1984): Formaldehyde in the British chemical industry: An occupational cohort study. Lancet i 611–616.

Ahmed, I, Whitson TC (1973): Formaldehyde: How much of a hazard? Ind Med and Surg 26–27.

Albert RE, Sellakumar AR, Laskin S, Kuschner M, Nelson A, Snyder CA (1982): Nasal cancer in the rat induced by gaseous formaldehyde and hydrogen chloride. J Natl Cancer Inst 68:597–603.

Blair A, Stewart P, O'Berg M, Gaffey W, Walrath J, Ward J, Bales R, Kaplan S, Cubit D (1986): Mortality among industrial workers exposed to formaldehyde. J Natl Cancer Inst 37(4):487–492.

Blejer HP, Miller BH (1966): Occupational health report of formaldehyde concentrations and effects on workers at the Bayly Manufacturing Company, Visalia, California. California Department of Public Health, Bureau of Occupational Health, Los Angeles, California, Study No. S–1806.

Environmental Protection Agency (1985): Formaldehyde determination of significant risk. Federal Register, 40 CFR Part 765.

Goldstein (1973): Textiles and the chemical industry: A marriage. J Am Assoc Textile Chemists and Colorists 10:209–214.

Harrington JM, Oakes D (1984): Mortality among British pathologists. Br J Ind Med 41:188–191.

Harrington JM, Shannon HS (1975): Mortality study of pathologists and medical laboratory technicians. Br Med J 4:329–332.

Hayes RB, Raatgever JW, de Bruyn A (1986): Tumors of the nose and nasal sinuses: A case-control study. Int J Cancer, 37:487–492.

Heck H (1982): Biochemical toxicology of inhaled formaldehyde. Chemical Industry Institute of Toxicology. 2(3): 3–8.

Levine RJ, Andjelkovitch DA, Shaw LK, Dal Corso RD (1984): Mortality of Ontario undertakers and a review of formaldehyde-related mortality studies. J Occ Med 26 740–746.

Liebling T, Rosenman KD, Pastides H, Griffith RG, Lemeshow S (1983): Mortality in relation to occupation: a study of workers at the Monsanto-Springfield chemical plant. Am J Ind Med 5 423–428.

Marsh GM (1982): Proportional mortality patterns among chemical plant workers exposed to formaldehyde. Br J Ind Med 39:313–322.

McMichael AJ (1976): Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. J Occup Med 18:165–168.

National Center for Health Statistics (1985): Vital Statistics of the U.S., Volume II—Mortality, Part A, Hyattsville, Maryland.

National Center for Health Statistics (1981): Health—United States 1981. DHHS Pub. No. (PHS) 82–1232. Hyattsville, Maryland.

National Institute for Occupational Safety and Health (1981a): Current Intelligence Bulletin 34. Formaldehyde: Evidence of Carcinogenecity. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH 45226.

National Institute for Occupational Safety and Health (1981b): NIOSH Manual of Analytical Methods; Vol. 7, P&CAM #354. DHHS (NIOSH) Publication No. 82–100. U.S. Government Printing Office, Washington, DC 20402.

Olsen JH, Jensen SP, Mogens H, Faurbo K, Breum NO, Jensen OM (1984): Occupational formaldehyde exposure and increased nasal cancer risk in man. Int J Cancer 34:639–644.

Schottenfeld D, Fraumeni JF (1982): Cancer Epidemiology and Prevention. W.B. Saunders Company, Philadelphia, PA.

Shipkovitz HD (1966): Formaldehyde vapor in the permanent-press fabrics industry. USDHEW, Public Health Service, Occupational Health Program, Cincinnati, Ohio. Report-TR–52.

Stayner LS, Smith AB, Reeve G, Blade L, Elliott L, Keenlyside R, Halperin W (1985): Proportionate mortality study of workers in the garment industry exposed to formaldehyde. Am J Ind Med 7:229–240.

Stroup NE (1984): A retrospective follow-up study of mortality in anatomists. Ph.D. Dissertation. Yale University, New Haven, Connecticut.

Swenberg JA, Kerns WD, Mitchell RE, Gralla EJ, Pavkov KL (1980): Induction of squamous cell carcinomas of the rat nasal cavity by inhalation exposure to formaldehyde vapor. Cancer Res 40:3398–3402.

U.S. Department of HEW (1979): Smoking and Health—A report of the Surgeon General. DHEW Pub. No. (PHS) 79–50066, 1979.

Vaughn TL, Strader C, Davis S, Daling JR (1986a): Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I. Occupational exposures. Int J Cancer 38:677–683.

Vaughn TL, Strader C, Davis S, Daling JR (1986b): Formaldehyde and cancers of the pharynx, sinus and nasal cavity: II. Residential exposures. Int J Cancer 38:685–688.

Walrath J, Fraumeni JF (1984): Cancer and other causes of death among embalmers. Cancer Res 44:4638–4641.

Walrath J, Fraumeni JF (1983): Mortality patterns among embalmers. Int J Cancer 31:407–411.

Waxweiler RJ, Beaumont JJ, Henry JA, Brown DP, Robinson CF, Ness GO, Wagoner JK, Lemen RA (1983): A modified life-table analysis system for cohort studies. J Occup Med 18:165–168.

Winn DM, Blott WJ, Shy CM (1981): Snuff dipping and oral cancer among women in the southern United States. N Engl J Med 304:745–749.

Wong O (1983): An epidemiologic mortality study of a cohort of chemical workers potentially exposed to formaldehyde, with a discussion on SMR and PMR. In "Formaldehyde Toxicity," J.E. Gibson, ed. Hemisphere Publishing, New York, pp 256–272.