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Proportionate Mortality Study of Workers in the Garment Industry Exposed to Formaldehyde

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In order to evaluate the human carcinogenicity of formaldehyde, we conducted a proportionate mortality study of garment workers engaged in the production of shirts from formaldehyde-treated cloth. This study included three plants, and was based upon 256 deaths identified from a death-benefit insurance fund. No deaths due to nasal cancer were observed, and the mortality from respiratory cancer (11 cases, PMR = 95) was slightly less than expected. Statistically significant ($p < .05$) elevations in proportionate mortality were observed for malignant neoplasms of the "buccal cavity" (three cases, PMR = 750), for "biliary passages and liver" (four cases, PMR = 313) and for "other lymphatic and hematopoietic sites" (four cases, PMR = 400). A proportionate cancer mortality (PCMR) analysis also was conducted, and cancer of the "buccal cavity" (three cases, PCMR = 682), and other "lymphatic and hematopoietic sites" (four cases, PCMR = 342) were still significantly elevated. The observed excesses in cancer mortality were primarily experienced by white females, who made up the major portion of the workforce, and workers with more than 10 years of latency and duration of exposure, a criterion for inclusion for most workers in the study group. The neoplasms observed were not equally distributed among the three facilities included in the study. Because of the small number of deaths involved and the lack of consistency with other studies, we believe that these findings should be viewed cautiously, pending the outcome of more definitive studies.

Key words: formaldehyde, cancer, garment workers

INTRODUCTION

Formaldehyde, commonly used as a disinfectant and tissue preservative, and as a feedstock in the synthetic chemical industry, has been shown to be carcinogenic in rodents. In a study conducted by the Chemical Industry Institute of Toxicology rats

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exposed by inhalation to 6 and 15 parts per million (ppm) of formaldehyde, and mice exposed to 15 ppm, developed squamous-cell carcinomas of the nasal passages [Chemical Industry Institute of Toxicology, 1982]. In experiments at New York University, inhalation of formaldehyde alone or in combination with hydrogen chloride induced squamous-cell nasal carcinomas in rats [Albert et al, 1982]. In addition, formaldehyde has been shown to be mutagenic in a number of cellular test systems [Auerbach et al, 1977] and is highly reactive with nucleic acids (DNA) and proteins [Feldman, 1975; Grafstrom et al, 1983].

A number of mortality studies of occupational groups exposed to formaldehyde have been initiated, and several have recently been completed [Wong, 1980; Walrath and Fraumeni, 1983; Levine et al, 1983; Fayerweather et al, 1982; Marsh, 1982; Liebling, 1982]. None of these studies have detected an association between formaldehyde exposure and either nasal or lung cancer. These studies were all extremely limited in their ability to detect an excess of nasal cancer, even if such an association existed, because of small sample size, intermittent exposures, and insufficient documentation of exposures. A few of these studies have detected statistically significant ($p < .05$) excesses of other cancers. In particular, excesses of prostatic cancer among formaldehyde production workers [Wong, 1980], cancers of the skin, kidney, and brain among embalmers [Walrath and Fraumeni, 1983], and cancers of the buccal cavity-pharynx and colon among workers involved in the production of formaldehyde resins [Liebling et al, 1982] have been observed. Because of the inconsistency between the observations from these investigations and other studies of formaldehyde-exposed workers, their findings must be viewed as inconclusive.

BACKGROUND

In 1979, we initiated a survey of workers exposed to formaldehyde in various industries in order to identify a suitable population for an epidemiologic study. The results of the survey suggested that garment workers, who are exposed to the offgassing of formaldehyde from cloth treated with formaldehyde resins, would be a suitable group for study. This group was relatively large, had reasonably continuous exposures, and was not known to be exposed to other potentially carcinogenic agents at the work site [Elliott, 1980; Elliott and Phillips, 1983]. The study was planned to have two phases: an initial phase consisting of a proportionate mortality study (PMR), followed by a retrospective cohort mortality study. Following are the findings from the initial phase (PMR) of this investigation.

MATERIALS AND METHODS

This study is based upon deaths reported to a death-benefit insurance fund for three shirt-manufacturing facilities, which will be henceforth referred to as facilities A, B, and C. This insurance fund is jointly operated by the union and companies involved. Plants B and C are located in Pennsylvania, and plant A is located in Georgia. These facilities produce shirts from cloth, which is received pretreated with formaldehyde resins to impart crease resistance, color fastness, and shrink resistance. Workers in these facilities are currently exposed to small amounts of formaldehyde which off-gasses from the cloth. All three sites have used formaldehyde-treated fabrics since 1958. Formaldehyde measurements recently taken at plants A and B

indicate that virtually all of the employees working in the production of these garments are exposed to air levels that range from 0.1 to 1.0 ppm. Past exposures to formaldehyde, although undocumented, are believed to have been higher, since improvements in the resin systems used have greatly reduced the amount of free formaldehyde contained in the cloth. No other potentially confounding chemical exposures were observed in these facilities [Elliott, 1980; Elliott and Phillips, 1983].

Workers whose survivors are eligible for death benefits were included in this study if they met one of the following criteria: (1) worked at least 6 months and died within 6 months of the last date worked; (2) worked at least 6 months and were disabled on the job; or (3) retired between age 62 and 65 and had worked at least 20 years if retirement was prior to 1975, or for 10 years if retirement was after 1976.

Deaths for inclusion in this study were identified at the insurance fund by the number of the local union that represented these facilities. A total of 304 death benefit files for individuals from these locals dying between January 1, 1959 and March 23, 1982 (date of record copying) were copied. However, 48 of these deaths were subsequently eliminated, 23 because their last date of union membership was prior to 1958, the year formaldehyde-treated cloth was first introduced in these plants, and 24 because they had never worked at the study facilities. Although these individuals did belong to a union local which represented one of the study sites, this local also represented other garment facilities that were not included in the study. Finally, one subject was eliminated because we were unable to obtain this person's death certificate, resulting in a final study size of 256 deaths. The underlying cause of death was coded by a nosologist using the revision of the International Classification of Diseases in effect at the time of death.

A proportionate mortality (PMR) analysis was performed using a computer program developed at NIOSH [Waxweiler et al, 1983]. This program computes a proportionate mortality ratio by dividing the number of deaths observed in cause-specific categories, by the number of deaths expected based upon the proportion of deaths in this category in the U.S. general population. The PMR is standardized for the potentially confounding effects on mortality of sex, race, age, and calendar time. The PMR analysis was stratified by duration of exposure (years exposed), latency (years since first exposure until death), and plant site. For duration and latency, exposure was assumed to begin either on the date of initiation into the union, or January 1, 1958, which ever occurred later. Exposure was assumed to have ended on the last date of membership in the union.

A proportionate cancer mortality (PCMR) analysis also was performed. This analysis is essentially the same as the PMR analysis, except that the analysis is restricted to cancer deaths alone. This analysis is useful because it has been demonstrated that cancer mortality rates of working population are usually less affected by the "healthy worker effect" than are mortality rates for the nonmalignant causes of death [McMichael, 1976]. A potential bias in the proportionate mortality ratio is often introduced by a deficit in cardiovascular diseases and other causes of death which are subject to the "healthy worker effect," thereby inflating the PMR for other causes of death, and particularly for malignant neoplasms.

The statistical significance of the PMRs and PCMRs was tested using a Fisher's exact test based upon the Poisson distribution. A one-tailed p-value of 0.05 was used as the minimum criterion for statistical significance. Ninety percent Fisher exact confidence limits were also computed. Statistical tests, confidence limits, and PMRs were not calculated for death categories containing only one observed death.

RESULTS

The frequency distributions of deaths according to sex, race, plant site, age at death, and duration of employment are presented in Table I. The study population was predominantly white (95%), female (75%), from plant A (59%), and over 55 (67%) at the time of death. Given the eligibility requirements for death benefits discussed earlier, it was not surprising that duration of employment was generally long, with a median of 20 years.

Table II presents the overall mortality experience for the study population. No deaths due to nasal cancer were observed in this investigation. Statistically significant excesses in mortality were observed for cancers of the buccal cavity (three cases, PMR = 750), biliary passages and liver (four cases, PMR = 313), and other lymphatic and hematopoietic sites (four cases, PMR = 400). All three of the buccal cavity malignancies were cancers of the parotid gland. One of these deaths was an epidermoid cell carcinoma, another was an adenocarcinoma, and the third did not have any histology specified on the death certificate. Hospital pathology reports were requested for all three deaths. However, only one report was obtainable, which confirmed the case of epidermoid cancer. Three of the tumors in the category of biliary passages and liver were cancers of the gall bladder, and the fourth was cancer of the bile duct. In the category of "other lymphatic and hematopoietic sites," three of the deaths were multiple myelomas and the fourth was a diffuse poorly differentiated lymphoma. Statistically nonsignificant excesses in mortality were evident in many of the malignant categories. There were fewer deaths observed than expected

TABLE I. Distribution of Deaths According to Sex, Race, Plant Site, Age at Death, and Duration of Employment

Variable	Frequency	Percent
Sex		
Male	64	25.0
Female	192	75.0
Race		
White	244	95.3
Black	11	4.3
Unknown	1	0.4
Plant site		
A	150	58.6
B	55	21.5
C	51	19.9
Age at death		
18–35	10	3.9
36–55	73	28.5
56–75	144	56.3
75+	29	11.3
Duration of employment		
0–5	23	9.0
6–10	24	9.4
11–15	46	14.1
16–20	36	18.0
21+	127	49.6

TABLE II. Proportionate Mortality Ratios (PMR) for all Causes of Death*

Cause of death	Observed (O)	Expected (E)	PMR (O/E × 100)	90% Confidence limits
All malignant neoplasms	87	73.26	118	99, 142
Buccal cavity and pharnyx	3	1.31	229	62, 592
Buccal cavity	3	.40	750[a]	204, 1939
Digestive organs and peritoneum	22	17.49	126	85, 180
Esophagus	1	.90	—	—
Stomach	2	2.27	88	16, 277
Intestine except rectum	8	7.32	109	54, 197
Biliary passages and liver	4	1.28	313[b]	107, 715
Liver not specified	2	.47	426	76, 1340
Pancreas	4	3.27	122	42, 280
Peritoneum and digestive organs	1	.27	—	—
Respiratory system	11	12.20	90	53, 157
Trachea, bronchus and lung	11	11.62	95	53, 157
Breast	17	14.58	117	74, 175
Female genital organs	12	9.96	120	69, 195
Urinary organs	2	2.17	92	16, 290
Other and unspecified sites	10	9.41	106	58, 180
Skin	2	1.12	179	32, 562
Brain and other parts nervous system	1	2.14	—	—
Connective tissue	1	.33	—	—
Other unspecified sites	6	5.83	103	45, 203
All lymphatic and hematopoietic	10	6.13	163	88, 277
Lymphosarcoma and reticulosarcoma	1	2.05	—	—
Hodgkin's disease	1	.70	—	—
Leukemia and aleukemia	4	2.38	168	57, 385
Other lymphatic and hematopoietic	4	1.00	400[b]	137, 915
Benign neoplasms of the brain	1	.77	—	—
Diabetes mellitus	5	5.69	88	35, 185
Diseases of blood and blood forming organs	1	1.03	—	—
Diseases of nervous system and sense organs	21	21.03	100	67, 144
Diseases of the circulatory system	93	89.84	104	87, 123
Respiratory diseases	14	11.87	118	71, 184
Diseases of the digestive system	1	9.89	—	—
Diseases of the genito-urinary system	2	2.91	69	12, 216
Diseases of the bones and organs of movement	1	.46	—	—
External causes of death	19	20.69	92	60, 135
Unknown causes	1	3.06	—	—
Other causes	10	15.46	65	35, 110

*PMRs were not calculated for death categories containing only one observed death. Standardized for age, sex, race, and calendar time.

[a]$p < .01$ (one tail).

[b]$p < .05$ (one tail).

in a few cancer sites; respiratory system (11 cases, PMR = 90), stomach (two cases, PMR = 88), and urinary organs (two cases, PMR = 92). There was a slight excess in mortality due to diseases of the circulatory system (93 cases, PMR = 104), and respiratory system (14 cases, PMR = 118). Marked deficits in mortality were observed for diseases of the digestive system (one observed vs 9.9 expected), and other causes of death (ten observed vs 15.46 expected).

The results from the proportionate cancer mortality analyses are presented in Table III. Generally, the magnitude of the excesses for malignant neoplasms observed in Table II was reduced by using this approach. Statistically significant excesses remained, however, for cancers of the buccal cavity (three cases, PCMR = 682) and for the category of other lymphatic and hematopoietic sites (four cases, PCMR = 342). Cancer of the biliary passages and liver was still in excess (four cases, PCMR = 274) but not statistically significant.

The proportionate mortality analysis for selected malignancies was stratified by sex and race (Table IV). The pattern in cancer mortality observed for the entire study group (Table II) was mirrored by the white female category. White women had a statistically significant excess in mortality due to cancers of the buccal cavity (two cases, PMR = 738) and the other lymphatic and hematopoietic category (three cases, PMR = 387). White women also had a nonsignificant excess of cancers of the biliary

TABLE III. Proportionate Cancer Mortality Ratios (PCMR) for all Malignant Neoplasms*

Cause of death	Observed (O)	Expected (E)	PMR (O/E × 100)	90% Confidence limits
Buccal cavity and pharynx	3	1.44	208	57, 538
Buccal cavity	3	.44	682[a]	185, 1758
Digestive organs and peritoneum	22	20.19	109	74, 156
Esophagus	1	.99	—	—
Stomach	2	2.57	78	14, 245
Intestine	8	8.61	93	46, 168
Biliary passages and liver	4	1.46	274	94, 627
Liver not specified	2	.54	370	66, 1166
Pancreas	4	3.74	107	37, 246
Peritoneum and digestive organs	1	.33	—	—
Respiratory system	11	13.14	84	47, 139
Trachea, bronchus and lung	11	12.53	88	49, 145
Breast	17	19.27	88	56, 132
Female genital organs	12	13.20	91	52, 147
Urinary organs	2	2.34	85	15, 269
Skin	2	1.33	150	27, 473
Brain and other parts nervous system	1	2.52	—	—
Connective tissues	1	.38	—	—
Other and unspecified sites	6	6.23	96	42, 190
All lymphatic and hematopoietic	10	6.94	144	78, 244
Lymphosarcoma and reticulosarcoma	1	2.37	—	—
Hodgkin's disease	1	.76	—	—
Leukemia and aleukemia	4	2.64	152	52, 347
Other lymphatic and hematopoietic	4	1.17	342[b]	117, 782

*PCMRs were not calculated for categories containing only one observed death. Standardized for age, sex, race and calendar time.
[a]$p < .01$ (one tail).
[b]$p \leq .01$ (one tail).

TABLE IV. Proportionate Mortality Ratios (PMR) for Selected Cancer Sites by Sex/Race Categories*

Cause of death	White female		White male		Black female		Black male	
	OBS	PMR	OBS	PMR	OBS	PMR	OBS	PMR
All malignancies combined	74	126[a]	8	68	4	338[a]	1	—
Buccal cavity and pharynx	2	234	1	—	0	—	0	—
Buccal cavity	2	738[a]	1	—	0	—	0	—
Digestive organs and peritoneum	19	139	2	62	1	—	0	—
Biliary passages and liver	3	287	1	—	0	—	0	—
Respiratory system	8	109	2	46	1	—	0	—
Trachea, bronchus and lung	8	114	2	49	1	—	0	—
Breast	16	111	9	—	1	—	0	—
Female genital organs	12	123	-	—	0	—	0	—
Urinary organs	1	—	0	—	0	—	1	—
Skin	1	—	12	—	0	—	0	—
Brain and other parts nervous system	1	—	0	—	0	—	0	—
Connective tissues	1	—	0	0	—	0	—	
Other and unspecified sites	6	175	0	—	0	—	0	—
All lymphatic and hematopoietic	7	144	2	178	1	—	0	—
Leukemia and aleukemia	3	160	1	—	0	—	0	—
Other lymphatic and hematopoietic	3	387[a]	0	1	—	0	—	

*PMRs were not calculated for categories containing only one observed death.
Standardized for age and calendar time.
[a]$p < .05$ (one tail).

passages and liver (three cases, PMR = 287). A statistically significant excess in mortality due to all malignant neoplasms combined was evident for both white (74 cases, PMR = 126), and black (four cases, PMR = 338) women.

In Table V the proportionate mortality experience of the study population is subdivided by plant site. Plant A had statistically significant excesses in cancer mortality due to all lymphatic and hematopoietic sites (eight cases, PMR = 234), and for the other lymphatic and hematopoietic sites (three cases, PMR = 507), in both instances reflecting the unusual finding of multiple myeloma at this site. Plant B had a statistically significant excess in mortality due to cancer of the buccal cavity (two cases, PMR = 2484) since two of the parotid tumors had occurred among employees at this location. Plant C had a statistically significant excess of cancer of the biliary passages and liver (two cases, PMR = 823) resulting from two cases of gall bladder cancer.

In Table VI the mortality experience of the study population is examined with regard to latency and duration of exposure. Statistically significant excesses were present in the category of greater than 10 years of latency and duration of exposure for all malignancies combined (51 cases, PMR = 137), buccal cavity cancer (two cases, PMR = 952), malignancies of the biliary passages and liver (three cases, PMR = 467), malignancies of all lymphatic and hematopoietic sites (eight cases, PMR = 283), and for malignancies of other lymphatic and hematopoietic sites (four cases, PMR = 761). There was also a statistically significant excess in mortality due to malignancies of the digestive organs and peritoneum (PMR = 194) in the less than 10 years of latency and exposure category.

TABLE V. PMR Analyses of Selected Cancer Sites by Plant Location*

	Plant A		Plant B		Plant C	
Cause of death	OBS	PMR	OBS	PMR	OBS	PMR
All malignancies combined	48	115	19	119	20	128
Buccal cavity and pharynx	0	—	2	768[a]	1	—
Buccal cavity	0	—	2	2484[b]	1	—
Digestive organs and peritoneum	9	87	7	183	6	175
Biliary passages and liver	2	269	0	—	2	828[a]
Respiratory system	8	112	3	133	0	—
Trachea, bronchus and lung	8	118	3	139	0	—
Breast	9	111	3	90	5	155
Female genital organs	5	90	2	83	5	241
Urinary organs	2	155	0	—	0	—
Skin	1	—	0	—	1	—
Brain and other parts nervous system	1	—	0	—	0	—
Connective tissues	1	—	0	—	0	—
Other and unspecified sites	4	159	1	—	1	—
All lymphatic and hematopoietic	8	234[a]	1	—	1	—
Leukemia and aleukemia	3	228	0	—	1	—
Lymphatic and hematopoietic	3	507[a]	—	0	—	

*PMRs were not calculated for categories containing only one observed death.
Standardized for age, sex, race, and calendar time.
[a]$p < .05$ (one tail).
[b]$p < .01$ (one tail).

DISCUSSION

Based upon the findings of the rat inhalation studies [Chemical Industry Institute of Toxicology, 1982; Albert et al, 1982], nasal cancer was considered a priori to be the most likely cancer site to be affected by formaldehyde. No cases of nasal cancer were observed in this investigation. These findings are consistent with the results from other mortality studies of formaldehyde exposed workers [Wong, 1980; Walrath and Fraumeni, 1983; Levine et al, 1983; Fayerweather et al, 1982; Marsh, 1982]. However, due to sample size, this study only had a 20% chance (power) of detecting a twofold excess for this rare tumor site (alpha = .05). In addition to statistical power, this study may not have observed any cases of nasal cancer because the latency period was too short, or because the intensity of formaldehyde exposures was too low. This study was also negative for respiratory cancer, for which there were fewer cases observed than expected (11 vs 12.2).

In this study, statistically significant elevations in proportionate mortality were observed for malignant neoplasms of the buccal cavity (three cases, PMR = 750) due to an excess of cancers of the parotid gland, for biliary passages and liver (four cases, PMR = 313) due to an excess of cancers of the gallbladder, and for other lymphatic and hematopoietic sites (four cases, PMR = 400) due to an excess of multiple myelomas. These excesses are based upon relatively small numbers of deaths (three or four), making the estimates of relative risk (PMRs) imprecise, as reflected by the wide confidence intervals for these sites in Table II.

The increased mortality in certain cancer sites in the PMR analyses was also evident in the proportionate cancer mortality (PCMR) analysis. However, the magnitude of these excesses was reduced in this analysis and the findings were only statistically significant for buccal cavity (PCMR = 682), and other lymphatic and

TABLE VI. PMR Analyses of Selected Cancer Sites by Duration of Exposure and Latency*

	Latency < 10 years and duration < 10 years		Latency ⩾ 10 years and duration < 10 years		Latency ⩾ 10 years and duration ⩾ 10 years	
Cause of death	(OBS)	(PMR)	(OBS)	(PMR)	(OBS)	(PMR)
All malignancies (MN) combined	28	103	8	68	51	137[a]
Buccal cavity and pharynx	1	—	0	—	2	286
Buccal cavity	1	—	0	—	2	952[b]
Digestinve organs and peritoneum	10	194[a]	1	29	11	124
Biliary passages and liver	1	—	0	—	3	467[a]
Respiratory system	5	154	3	160	3	42
Trachea, bronchus, and lung	5	163	2	112	3	44
Breast	3	56	2	109	12	163
Female genital organs	5	127	0	—	7	148
Urinary organs	0	—	1	—	1	—
Skin	1	—	0	—	1	—
Brain and other parts of nervous system	1	0	—	0	—	—
Connective tissue	0	—	0	—	1	—
Other and unspecified sites	0	—	1	—	5	200
All lymphatic and hematopoietic	2	88	0	—	8	283[b]
Leukemia and aleukemia	2	217	0	—	2	192
Other lymphatic and hematopoietic	0	—	0	—	4	761[b]

*For both latency and duration of exposure, exposure was assumed to start either on the date of initiation into the union or 1/1/58, whichever occurred later. Latency is the time from first exposure until death; duration of exposure is the time between the first and last date of exposure. PMRs were not calculated for categories containing only one observed death. No cancer deaths were observed with latency < 10 years and duration ⩾ 10 years. Standardized for the effects of age, sex, race, and calendar time.

[a]$p < .05$ (one tail).

[b]$p < .01$ (one tail).

hematopoietic sites (PCMR = 342). The fact that these sites were significantly elevated in this analysis indicates that the excesses of these sites observed in the PMR analysis can not be fully attributed to deficits in the nonmalignant causes of death inflating the PMRs for malignant sites.

The observed excess in cancer mortality was most pronounced among white females, who made up the major portion of the study population (73%). The fact that the observed excesses were primarily among workers with greater than 10 years of latency and exposure supports the hypothesis that these findings could be related to occupational exposure to formaldehyde, since the induction of cancer in humans is usually related to duration of exposure and requires a long period of time from first exposure to the development of the disease (latency). Alternatively, these observations may be explained by the fact that the majority of the study subjects had more than 10 years of latency and duration of exposure because of the eligibility requirements for receiving death benefits. It is worth noting that the maximum latency achievable in this study was 24 years and that this study would be unable to detect an excess of cancer if there were a longer latency period than the 24 years covered by this study.

The excesses in cancer mortality were unevenly distributed among the plant facilities. The parotid gland tumor excess was from plant B, the gall bladder and biliary passages cancer excess was from plant C, and the multiple myeloma excess was from plant A. Based upon our industrial hygiene survey results, we believe that

the processes and formaldehyde exposures were very similar at these facilities [Elliott, 1980; Elliott and Phillips; 1983). This differential in cancer site excesses among the plant locations, despite relatively uniform exposure to formaldehyde, argues against the hypothesis that these excesses were related to formaldehyde exposures. On the other hand, because of the small study size of each of the plant locations, the statistical power of each location for these cancer sites was exceedingly low.

Significant elevations in mortality due to the cancer sites observed have not been consistently observed in other studies of formaldehyde-exposed workers, although excesses of oral pharyngeal and lymphatic cancer have been observed in a few of these studies. A statistically significant ($p < .01$) increase in risk due to lymphatic and hematopoietic neoplasms (SMR = 242) was observed in a mortality study of British pathologists [Harrington and Shannon, 1975]. In a PMR study of New York State embalmers and funeral directors, Walrath and Fraumeni [1983] observed a twofold (nonsignificant) increase in mortality due to cancers of the buccal cavity and pharynx (PMR = 201) among persons licensed only as embalmers. Six of the seven deaths in this category were malignancies of the buccal cavity, and one was a salivary gland tumor [personal communication of J. Walrath]. According to U.S. Vital Statistics among white males in 1975, only 30% of the deaths in the category of buccal-pharyngeal cancer were due to cancers of the buccal cavity. Thus, if the analysis had been restricted in the Walrath study to buccal cavity cancer, a much larger increase in mortality would probably have been observed. In our study, however, the tumor type was parotid gland, which is not entirely consistent with the types observed in Walrath's study. Finally, Liebling et al [1982] in a PMR study of chemical workers observed a statistically significant ($p < .05$) excess of cancer of the buccal cavity and pharynx (PMR = 870) among a high formaldehyde exposure group. However, this excess was based upon only two cases (nasopharyngeal and floor of the mouth), again different from the parotid tumors observed in this investigation.

The observation that all three of the buccal cavity cancers were parotid gland neoplasms is highly unusual. According to U.S. Vital Statistics for 1970, among white females only 16% of buccal cavity cancers were parotid gland tumors. Despite this fact, the biologic plausibility of this finding being causally linked to formaldehyde is limited. Cancers experimentally induced in rats by formaldehyde inhalation have involved the tissues receiving direct contact with formaldehyde (nasal cavity). In laboratory rats, which are obligate nose-breathers, the principal site of formaldehyde absorption is the nasal epithelium [Heck, 1982]. In humans, who can be either nasal- or mouth-breathers, the tissue primarily receiving exposure can be either the nasal or oral epithelium. However the parotid gland is internal to the oral cavity and communicates with it by a pair of salivary ducts. Given the rapid metabolism of formaldehyde to formic acid at the site of absorption [Heck, 1982] and the location of the parotid glands, it is speculative as to whether or not any formaldehyde reaches the parotid gland. It is even harder to comprehend how internal sites such as the gallbladder and the lymph system could receive significant doses of formaldehyde.

There is, as always, the possibility that the excesses observed in this investigation could either be the result of confounding variables that were not accounted for in the analysis or be due to chance. Since a large number of causes of death were examined in these analyses a few causes would be expected to be significantly elevated on the basis of chance alone. Although tobacco usage and alcohol consumption have

been associated with cancers of several buccal cavity sites, these relationships do not apply to cancer of the parotid gland, for which there are no known etiologic risk factors [Frie and Holland, 1982]. In addition, the fact that lung cancer was not elevated in this study indicates that smoking is unlikely to have contributed to the observed excess of buccal cavity cancer. Multiple myeloma has been associated with exposure to radiation, asbestos, and heavy metals and with employment in the rubber, petrochemical, furniture, leather, and food industries [Schottenfeld and Fraumeni, 1982]. Gallbladder cancers have been associated with a history of gallstones [Frie and Holland, 1982]. We are unaware of any environmental exposures in these plants, or other factors which could explain the observed excesses, although unrecognized factors such as diet or ethnicity could conceivably be responsible.

In summary, no nasal cancer deaths were observed, but statistically significant elevations in proportionate mortality were observed for cancers of the buccal cavity (parotid gland), biliary passages and liver (gallbladder), and other lymphatic and hematopoietic sites (multiple myeloma). The fact that these excesses occurred among workers with greater than 10 years of latency and exposure, and the fact that there are no other known environmental factors in these plants which could explain these observations, supports the hypothesis that these excesses are associated with formaldehyde exposure. Alternatively, the fact that elevations in mortality for these tumors have not been consistently observed in other studies of formaldehyde-exposed workers, the fact that these excesses were not consistently present in each of this investigation's plant locations, and the lack of biologic plausibility for these effects argues against this hypothesis. Because of these inconsistencies, and the small number of deaths involved, we believe that these positive findings should be viewed as tentative, and that conclusions on the human carcinogenicity of formaldehyde must await the results of more definitive investigations that are now in progress.

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