American Journal of Epidemiology
Vol. 159, No. 12
Printed in U.S.A.
DOI: 10.1093/aje/kwh174

Mortality from Solid Cancers among Workers in Formaldehyde Industries

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Received for publication December 1, 2003; accepted for publication March 16, 2004.

In industrial workers, formaldehyde exposure has been associated with cancer of the nasal cavities, nasopharynx, prostate, lung, and pancreas; however, these associations are inconsistent and remain controversial. Animals exposed to formaldehyde show excesses of nasal cancer. In an extended follow-up of a large cohort of formaldehyde-exposed workers, the authors evaluated mortality from solid cancers (1,921 deaths) among 25,619 workers (865,708 person-years) employed in 10 US formaldehyde-producing or -using facilities through 1994. Exposure assessment included quantitative estimates of formaldehyde exposure. Standardized mortality ratios and relative risks were calculated. Compared with that for the US population, mortality from solid cancers was significantly lower than expected among subjects exposed and nonexposed to formaldehyde (standardized mortality ratios = 0.91 and 0.78, respectively). Relative risks for nasopharyngeal cancer (nine deaths) increased with average exposure intensity, cumulative exposure, highest peak exposure, and duration of exposure to formaldehyde (p-trend = 0.066, 0.025, <0.001, and 0.147, respectively). Formaldehyde exposure did not appear to be associated with lung (744 deaths), pancreas (93 deaths), or brain (62 deaths) cancer. Although relative risks for prostate cancer (145 deaths) were elevated for some measures of formaldehyde exposure, the trend was inconsistent. In this cohort of formaldehyde-industry workers, some evidence was found of an exposure-response relation with mortality from nasopharyngeal cancer (based on small numbers) but not for cancers of the pancreas, brain, lung, or prostate.

carcinogens; cohort studies; formaldehyde; lung; mortality; nasopharynx; neoplasms; occupational health

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

The flammable and colorless gas formaldehyde (CH_2O) is used in the production of resins, molding compounds, photographic film, decorative laminates, and plywood and as a bactericide and tissue preservative. Approximately 1.5 million workers in the United States were exposed to formaldehyde in 1981 (1). Formaldehyde irritates the eye and upper airway mucosa at concentrations exceeding 0.5–1 ppm (2). In rats and mice, inhalation exposure has caused squamous cell carcinomas of the nasal cavity (3, 4).

In 1995, the International Agency for Research on Cancer found sufficient evidence for the carcinogenicity of formaldehyde in animals but only limited evidence for carcinogenicity in humans (2). Some studies of industrial workers or embalmers, pathologists, and anatomists have associated formaldehyde exposure with cancer of the nasal cavities (5–7), nasopharynx (5, 7–14), prostate (10, 15), lung (16–18), pancreas (19), brain (10, 15, 20–24), and lymphohematopoietic system (8, 10, 15, 17, 20, 23, 25, 26). However, these associations were inconsistent and remain controversial.

In this study, we assessed the relation between formaldehyde and selected solid cancers in an extended follow-up of the largest known cohort to date of industrial workers in formaldehyde industries. In a separate analysis of these data (27), we observed a significant association between mortality from leukemia, particularly myeloid leukemia, and peak and average exposure to formaldehyde.

MATERIALS AND METHODS

Cohort design and follow-up

Details of the original study design (5) and extended follow-up (27) have been described previously. In brief,

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25,619 US workers employed at 10 plants prior to January 1, 1966, were enrolled in the cohort (878 workers of unknown sex or race and 64 workers who started work after January 1, 1966, were excluded). Subjects were followed from the year of initial plant identification (i.e., the year in which employment records were thought to be complete; range, 1934–1958) or first employment at a plant, whichever was later, through December 31, 1994. The Social Security Administration, the Health Care Financing Administration, the Veterans Administration, credit bureaus, motor vehicle departments, and telephone directories were used to determine vital status before 1980, and a National Death Index Plus search was used thereafter. Information on underlying cause of death was obtained for 8,486 deceased workers. For 866 subjects (3.4 percent) lost to follow-up prior to 1980, person-year accumulation ended at the last date known alive. These data were the basis for this analysis and for the evaluation of mortality from lymphohematopoietic malignancies reported separately (27), and they represent 15 years of additional mortality follow-up (resulting in a doubling of the number of deaths) compared with the previous analysis (5, 28).

On the basis of information from secondary sources other than death certificates, it was found that one of the nasopharyngeal cancer subjects had been misclassified on the death certificate and in fact had cancer of the tonsillar fossa (29). For this subject, nasopharyngeal cancer was used as the cause of death to calculate standardized mortality ratios, since population reference rates are based on death certificates, but cancer of the oropharynx, of which the tonsillar fossa is a part, was used to estimate relative risks.

Exposure assessment

We estimated exposure to formaldehyde from work histories through 1980 based on job titles, tasks, visits to the plants by study industrial hygienists, discussions with workers and plant managers, and monitoring data. Peak exposures were defined as short-term excursions (generally less than 15 minutes) that exceeded the 8-hour, time-weighted average formaldehyde intensity. Peak exposures in the workplace occurred from routine (e.g., hourly, daily, or weekly) or nonroutine performance of high-exposure tasks or from working in areas where nonroutine, unusual upsets or events, such as spills, occurred. Since no measurements of peak exposure were available in this study, peaks and their frequency (hourly, daily, weekly, or monthly) were estimated by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-weighted average. We assessed the presence of particulates to represent formaldehyde as a solid (e.g., paraformaldehyde or trioxane), formaldehyde-containing resins, molding compound particulates, or particulates onto which formaldehyde gas could be adsorbed. Exposures to 11 suspected carcinogens and other widely used chemicals in the plants were evaluated (antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, wood dust, and benzene). We also identified workers employed as chemists or laboratory technicians because of their potential exposure to various other chemicals. The exposure assessment is described in detail elsewhere (5, 30, 31). For the extended follow-up, no information on formaldehyde exposure after 1980 was obtained.

Statistical analysis

The following formaldehyde exposure metrics were calculated as time-dependent variables: cumulative exposure (ppm-years), average exposure intensity (ppm), duration of exposure (years), highest peak exposure category (nonexposed, >0–<0.5 ppm, 0.5–<2.0 ppm, 2.0–<4.0 ppm, ≥4.0 ppm), exposure to formaldehyde-containing particulates (ever/never), duration of exposure to each of 11 other substances (years), and duration of working as a chemist or laboratory technician (years). Workers contributed person-time to the nonexposed category until they were exposed. Then, they contributed person-time to the appropriate exposure categories depending on their levels of exposure. For each worker, we collapsed jobs in adjacent time periods of exposure for which all of the estimated exposure variables were identical. However, for the description of exposure levels in these jobs, nonadjacent periods with identical estimated exposures were counted separately.

Standardized mortality ratios and relative risks were estimated by using standard methods (32). Relative risks were based on Poisson regression models and were adjusted for calendar year, age, sex, race, and pay category (32). The low-exposure category was used as the reference to minimize the impact of any unmeasured confounding variables, since nonexposed workers may differ from exposed workers with respect to socioeconomic characteristics. However, workers in the low-exposure category were exposed to very low levels of formaldehyde. We evaluated confounding for exposure to other substances and for working as a chemist or laboratory technician. Tests of trend for categorical variables were based on the estimated slope of the corresponding continuous variable, except for peak exposure, where categorical ranks were used. Heterogeneity among risk estimates was assessed by likelihood ratio tests. Tests were two-sided at a 5 percent significance level. For details of the statistical analysis, refer to the separate report by Hauptmann et al. (27).

We calculated all exposures by using a 15-year lag interval to account for latency of solid cancers. Lag intervals from 2 to 20 years were evaluated, but no substantial differences for model fit from the 15-year lag were found for solid cancers of primary interest. The 15-year lag interval was eventually chosen because 15 years is commonly regarded as a minimum latency time for solid tumors and because it conforms to the lack of exposure information for the extension of the follow-up (1980–1994).

Since plant was correlated with exposure, we do not present relative risk estimates adjusted for plant in this paper. However, adjusting for plant did not substantially change the results.

TABLE 1. Demographic characteristics (no. of subjects) of the cohort of workers in US formaldehyde industries analyzed regarding mortality from solid cancers

Characteristic	Plant identification no. and year of cohort identification*										Total†
	Plant 1, 1943	Plant 2, 1945	Plant 3, 1949	Plant 4, 1958	Plant 5, 1957	Plant 6, 1951	Plant 7, 1938	Plant 8, 1934	Plant 9, 1956	Plant 10, 1941	
Race and sex											
White men	3,663	781	1,324	1,606	564	3,965	3,574	1,365	1,516	2,300	20,658 (81)
Black men	184	0	969	8	38	120	157	0	67	292	1,835 (7)
White women	413	3	81	78	133	1,151	496	313	349	83	3,100 (12)
Black women	1	0	1	0	9	12	1	1	1	0	26 (<1)
Year of entry into the cohort											
≤1945	572	43	0	0	0	0	1,295	486	0	709	3,105 (12)
1946–1955	2,339	522	774	0	0	3,261	1,961	795	0	1,548	11,200 (44)
1956–1965	1,350	219	1,601	1,692	744	1,987	972	398	1,933	418	11,314 (44)
Age at entry (years)											
≤30	2,657	532	1,650	921	306	3,358	3,047	1,052	1,521	1,833	16,877 (66)
31–40	942	201	457	446	178	1,066	727	303	242	560	5,122 (20)
41–50	473	48	216	284	172	549	336	206	111	198	2,593 (10)
51–60	169	3	44	33	72	199	97	91	52	78	838 (3)
≥61	20	0	8	8	16	76	21	27	7	6	189 (1)
Duration of follow-up (years)											
≤30	1,370	181	1,076	490	188	1,890	1,119	562	676	721	8,273 (32)
31–35	702	116	736	528	156	903	519	263	918	251	5,092 (20)
36–40	811	132	341	674	400	1,035	616	148	339	613	5,109 (20)
≥41	1,378	355	222	0	0	1,420	1,974	706	0	1,090	7,145 (28)
Vital status†											
Alive	2,401	500	1,514	1,236	611	3,254	2,906	915	1,489	1,441	16,267 (64)
Deceased	1,679 (39)	260 (33)	754 (32)	437 (26)	130 (17)	1,821 (35)	1,179 (28)	706 (42)	350 (18)	1,170 (44)	8,486 (33)
Unknown	181 (4)	24 (3)	107 (5)	19 (1)	3 (<1)	173 (3)	143 (3)	58 (3)	94 (5)	64 (2)	866 (3)
Total	4,261	784	2,375	1,692	744	5,248	4,228	1,679	1,933	2,675	25,619

* Year in which employment records were thought to be complete.
† Numbers in parentheses, percent.

RESULTS

Demographic description of the cohort

A total of 25,619 subjects entered the cohort between 1934 and 1966; 75 percent entered before 1960. Duration of follow-up ranged from a few days to 58 years, with a median duration of 35 years. The total number of person-years accrued was 865,708. The median ages at entry and exit were 26 and 64 years, respectively. The cohort consisted predominantly of White men (81 percent) and White women (12 percent) (table 1).

Exposure to formaldehyde

In jobs involving formaldehyde exposure, the median 8-hour time-weighted average formaldehyde intensity was 0.45 ppm (range, 0.01–4.25 ppm), and 16.6 percent of all jobs involved no exposure to formaldehyde. Average intensity was 2 ppm or higher for 2.6 percent of the jobs; for 14.3 percent of the jobs, peak exposures were 4 ppm or higher. Among exposed workers, median values for duration of jobs involving exposure to formaldehyde, average intensity of exposure, and cumulative exposure were 2 years (range, 0–46 years), 0.3 ppm (range, 0.01–4.25 ppm), and 0.6 ppm-years (range, 0.0–107.4 ppm-years), respectively. Of all workers in the cohort, 17.5 percent were never employed in jobs involving exposure to formaldehyde, 4.7 percent were ever employed in jobs in which average intensities were 2 ppm or higher, and 22.6 percent were ever employed in jobs involving peak exposures of 4 ppm or higher. Time-weighted average estimates were generally similar to or slightly higher than those from other reports on occupational exposures in the literature (33).

Cancer mortality and exposure to formaldehyde

Compared with that for the US population, mortality from solid cancers was significantly decreased in nonexposed

TABLE 2. Numbers of observed deaths and standardized mortality ratios with 95% confidence intervals for selected cancers and other major causes of death among US workers nonexposed and exposed to formaldehyde, mortality follow-up through 1994

Cause of death (ICD-8* code(s))	Nonexposed			Exposed†		
	Observed (no.)	SMR*	95% CI*	Observed (no.)	SMR	95% CI
All causes (001–999)	1,991	0.85	0.81, 0.89	6,495	0.96	0.94, 0.98
All cancer (140–209)	376	0.76	0.69, 0.84	1,723	0.90	0.86, 0.95
Solid cancer (140–199)	341	0.78	0.70, 0.86	1,580	0.91	0.87, 0.96
Benign/unspecified neoplasms (210–239)	6	0.70	0.31, 1.55	21	1.14	0.74, 1.74
Circulatory system (390–458)	815	0.77	0.72, 0.83	3,030	0.88	0.85, 0.91
Respiratory diseases (460–519)	84	0.59	0.48, 0.73	460	0.82	0.75, 0.90
Cancer						
Buccal cavity (140–149)	13	0.99	0.58, 1.71	49	1.01	0.77, 1.34
Nasopharynx (147)	2	1.56	0.39, 6.23	8	2.10	1.05, 4.21‡
Digestive system (150–159)	97	0.74	0.61, 0.91	420	0.89	0.80, 0.97
Liver (155–156)	8	0.75	0.38, 1.51	23	0.68	0.45, 1.03
Pancreas (157)	14	0.59	0.35, 0.99	79	0.83	0.67, 1.04
Respiratory system (160–163)	110	0.80	0.66, 0.96	668	0.97	0.90, 1.04
Nose and nasal cavity (160)	0	0.00	0.00, 2.01	3	1.19	0.38, 3.68
Larynx (161)	6	1.05	0.47, 2.35	23	0.95	0.63, 1.43
Lung (162)	103	0.79	0.65, 0.96	641	0.97	0.90, 1.05
Bone (170)	0	0.00	0.00, 0.66	7	1.57	0.75, 3.29
Skin (172–173)	5	0.48	0.20, 1.15	29	0.82	0.57, 1.18
Breast (174)	16	0.66	0.41, 1.08	19	0.59	0.38, 0.92
Female genital (180–184)	16	1.00	0.61, 1.63	14	0.74	0.44, 1.25
Prostate (185)	14	0.59	0.35, 0.99	131	0.90	0.75, 1.06
Bladder (188)	6	0.56	0.25, 1.25	31	0.68	0.48, 0.97
Kidney (189)	11	1.00	0.56, 1.81	37	0.81	0.58, 1.11
Brain and central nervous system (191–192)	19	1.09	0.70, 1.71	43	0.92	0.68, 1.23
Person-years	409,074			456,634		

* ICD-8, *International Classification of Diseases*, Eighth Revision; SMR, standardized mortality ratio; CI, confidence interval.

† Exposure status was calculated by using a 15-year lag interval.

‡ The exact 95% confidence interval is 0.91, 4.14.

(standardized mortality ratio (SMR) = 0.78) and exposed (SMR = 0.91) workers (table 2). Significant deficits occurred for cancers of the digestive system, pancreas, lung, bone, and prostate in the nonexposed and for cancers of the digestive system, breast, and bladder in the exposed. Excesses among exposed workers were observed for cancers of the nasopharynx, nose and nasal cavity, and bone. On the basis of the relative risks, no consistent evidence of increasing risks was found for mortality from all solid cancers combined with any measure of formaldehyde exposure (tables 3, 4, 5, and 6).

Extension of the follow-up (1980–1994) added 466 lung cancers to the 278 cases from the original follow-up (1960–1980). On the basis of the relative risks, there was no evidence of an association between formaldehyde exposure and lung cancer mortality (tables 3, 4, 5, and 6). We found no association between lung cancer mortality and average, peak, and cumulative formaldehyde exposure within subgroups of age, pay category, or exposure to formaldehyde-containing particulates (table 7) (data for peak and cumulative exposure not shown). To evaluate risk of lung cancer by cumulative exposure in more detail, we divided the highest exposure category into additional categories: 5.5–7.9, 8.0–11.9, 12.0–15.9, and ≥16.0 ppm-years. The respective relative risks for these categories, compared with those for workers exposed to low levels (>0–<1.5

TABLE 3. Relative risks and numbers of deaths for selected cancers and other major causes of death by average intensity of exposure to formaldehyde, United States, mortality follow-up through 1994

Cause of death (ICD-8* code(s))	Average intensity of exposure (ppm)†								*p*-trend‡	*p*-trend§
	0		>0–<0.5¶		0.5–<1.0		≥1.0			
	Relative risk#	No. of deaths	Relative risk#	No. of deaths	Relative risk#	No. of deaths	Relative risk#	No. of deaths		
All causes (001–999)	1.01	1,991	1.00	3,640	1.12**	1,405	1.04	1,450	0.608	0.733
All cancer (140–209)	0.99	376	1.00	953	1.17**	383	1.10	387	0.183	0.217
Solid cancer (140–199)	1.01	341	1.00	880	1.15**	349	1.07	351	0.432	0.439
Benign/unspecified neoplasms (210–239)	0.43	6	1.00	12	0.72	3	1.31	6	0.052	0.075
Circulatory system (390–458)	0.99	815	1.00	1,709	1.13**	670	0.98	651	–0.156	–0.101
Respiratory diseases (460–519)	0.92	84	1.00	260	1.11	102	0.96	98	–0.908	–0.814
Cancer										
Upper respiratory tract†† (142, 144, 145, 147, 160, 161)	1.47	11	1.00	18	1.69	11	2.21**	15	0.158	0.122
Buccal cavity (140–149)	2.42**	13	1.00	18	2.41**	16	1.89	15	0.791	0.504
Salivary gland (142)	NA*	0	NA	0	NA	4	NA	0	0.592	0.641
Nasopharynx‡‡ (147)	1.00§§	2	NA	0	0.38	1	1.67	6	0.126	0.066
Digestive system (150–159)	0.92	97	1.00	257	0.93	82	0.84	81	–0.215	–0.237
Liver (155–156)	1.54	8	1.00	12	0.82	3	2.05	8	0.584	0.219
Pancreas (157)	0.76	14	1.00	48	0.72	12	1.05	19	0.998	–0.889
Respiratory system (160–163)	1.03	110	1.00	362	1.14	146	1.16	160	0.873	0.726
Nose and nasal cavity (160)	NA	0	1.00	2	1.48	1	NA	0	–0.802	–0.562
Larynx (161)	1.09	6	1.00	11	1.00	4	2.02	8	0.284	0.263
Lung (162)	1.04	103	1.00	348	1.15	141	1.14	152	0.760	0.843
Bone (170)	NA	0	1.00	2	2.91	2	4.37	3	0.109	0.189
Skin (172–173)	0.29	5	1.00	15	1.63	8	1.31	6	0.328	0.673
Breast (174)	1.27	16	1.00	14	0.49	2	0.65	3	–0.183	–0.492
Female genital (180–184)	1.18	16	1.00	8	1.30	3	1.21	3	0.901	0.804
Prostate (185)	0.67	14	1.00	72	1.27	31	1.18	28	0.031	0.065
Bladder (188)	1.06	6	1.00	14	1.76	9	1.42	8	0.596	0.634
Kidney (189)	1.39	11	1.00	20	1.48	10	0.91	7	0.992	0.842
Brain and central nervous system (191–192)	1.84	19	1.00	23	1.07	9	1.19	11	0.819	0.631
Person-years	409,074		279,992		88,074		88,568			

* ICD-8, *International Classification of Diseases*, Eighth Revision; NA, not applicable (a relative risk estimate for this category of exposure was not available because there was no death in this category or in the reference category).

† Exposure was calculated by using a 15-year lag interval.

‡ Likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure for nonexposed and exposed person-years; –, negative slope estimate.

§ Likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure for exposed person-years only; –, negative slope estimate.

¶ Reference for all categories.

Relative risk from Poisson regression analysis stratified by calendar year, age (both in 5-year intervals), sex, and race (Black/White) and adjusted for pay category (salary/wage).

** 95% confidence interval does not include 1.00.

†† Cancer of the salivary gland, floor of the mouth, other mouth, nasopharynx, nasal cavity, larynx.

‡‡ Cause of death corrected from cancer of the nasopharynx to that of the oropharynx for one death based on information from secondary sources other than death certificates (29).

§§ Reference for this site because of no cases in the low-exposure category.

TABLE 4. Relative risks and numbers of deaths for selected cancers and other major causes of death by peak exposure to formaldehyde, United States, mortality follow-up through 1994

Cause of death (ICD-8* code(s))	Peak exposure (ppm)†								*p*-trend‡	*p*-trend§
	0		>0–<2.0¶		2.0–<4.0		≥4.0			
	Relative risk#	No. of deaths	Relative risk#	No. of deaths	Relative risk#	No. of deaths	Relative risk#	No. of deaths		
All causes (001–999)	1.05	1,991	1.00	2,554	1.21**	1,945	1.07**	1,996	0.013	0.014
All cancer (140–209)	1.04	376	1.00	655	1.28**	534	1.09	534	0.078	0.114
Solid cancer (140–199)	1.04	341	1.00	612	1.24**	487	1.04	481	0.346	0.372
Benign/unspecified neoplasms (210–239)	0.61	6	1.00	6	1.47	6	2.22	9	0.043	0.143
Circulatory system (390–458)	1.04	815	1.00	1,191	1.21**	918	1.04	921	0.202	0.251
Respiratory diseases (460–519)	0.92	84	1.00	188	1.05	132	0.98	140	0.776	0.864
Cancer										
Upper respiratory tract†† (142, 144, 145, 147, 160, 161)	1.32	11	1.00	14	1.24	12	1.65	18	0.302	0.142
Buccal cavity (140–149)	2.08	13	1.00	15	1.07	11	1.83	23	0.433	0.072
Salivary gland (142)	NA*	0	NA	0	1.00‡‡	2	0.97	2	0.102	0.125
Nasopharynx§§ (147)	1.00‡‡	2	NA	0	NA	0	1.83	7	0.044	<0.001
Digestive system (150–159)	0.95	97	1.00	178	0.92	102	1.05	140	0.626	0.485
Liver (155–156)	1.94	8	1.00	7	1.54	6	2.18	10	0.481	0.045
Pancreas (157)	0.78	14	1.00	33	0.93	20	1.00	26	0.710	–0.920
Respiratory system (160–163)	1.06	110	1.00	249	1.43**	236	0.93	183	–0.813	–0.572
Nose and nasal cavity (160)	NA	0	1.00	1	1.55	1	1.47	1	0.414	0.779
Larynx (161)	0.86	6	1.00	10	1.19	8	0.64	5	–0.645	–0.514
Lung (162)	1.08	103	1.00	237	1.45**	227	0.94	177	–0.874	–0.669
Bone (170)	NA	0	1.00	2	0.70	1	2.55	4	0.063	0.256
Skin (172–173)	0.30	5	1.00	10	1.85	12	0.96	7	0.145	0.924
Breast (174)	1.28	16	1.00	12	0.52	4	1.00	3	–0.282	0.865
Female genital (180–184)	1.32	16	1.00	6	1.29	5	1.89	3	0.687	0.296
Prostate (185)	0.73	14	1.00	47	1.61**	42	1.14	42	0.170	0.568
Bladder (188)	1.18	6	1.00	9	1.63	10	1.74	12	0.247	0.304
Kidney (189)	1.34	11	1.00	15	1.23	12	0.89	10	–0.585	–0.791
Brain and central nervous system (191–192)	1.64	19	1.00	18	1.06	14	0.74	11	–0.162	–0.405
Person-years	409,074		209,815		121,729		125,090			

* ICD-8, *International Classification of Diseases*, Eighth Revision; NA, not applicable (a relative risk estimate for this category of exposure was not available because there was no death in this category or in the reference category).

† Exposure was calculated by using a 15-year lag interval.

‡ Likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure for nonexposed and exposed person-years; –, negative slope estimate.

§ Likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure for exposed person-years only; –, negative slope estimate.

¶ Reference for all categories.

Relative risk from Poisson regression analysis stratified by calendar year, age (both in 5-year intervals), sex, and race (Black/White) and adjusted for pay category (salary/wage).

** 95% confidence interval does not include 1.00.

†† Cancer of the salivary gland, floor of the mouth, other mouth, nasopharynx, nasal cavity, larynx.

‡‡ Reference for this site because of no cases in the low-exposure category.

§§ Cause of death corrected from cancer of the nasopharynx to that of the oropharynx for one death based on information from secondary sources other than death certificates (29).

ppm-year), were 0.91, 0.99, 0.84, and 0.64. Similarly, dividing the highest exposure category for exposure intensity—1.0–1.4, 1.5–1.9, 2.0–2.4, and ≥2.5 ppm—resulted in relative risks of 1.26, 0.86, 1.42, and 0.77, respectively, compared with >0–<0.5 ppm. These results were similar when the analysis was restricted to wage workers only. No

TABLE 5. Relative risks and numbers of deaths for selected cancers and other major causes of death by cumulative exposure to formaldehyde, United States, mortality follow-up through 1994

Cause of death (ICD-8* code(s))	Cumulative exposure (ppm-year)†								*p*-trend‡	*p*-trend§
	0		>0–<1.5¶		1.5–<5.5		≥5.5			
	Relative risk#	No. of deaths	Relative risk#	No. of deaths	Relative risk#	No. of deaths	Relative risk#	No. of deaths		
All causes (001–999)	0.97	1,991	1.00	3,951	0.96	1,324	1.03	1,220	–0.574	–0.271
All cancer (140–209)	0.94	376	1.00	1,038	0.95	352	1.02	333	0.942	–0.865
Solid cancer (140–199)	0.97	341	1.00	950	0.97	328	1.01	302	–0.852	–0.725
Benign/unspecified neoplasms (210–239)	0.40	6	1.00	13	0.63	3	1.22	5	0.808	0.967
Circulatory system (390–458)	0.97	815	1.00	1,804	0.98	640	1.05	586	–0.496	–0.335
Respiratory diseases (460–519)	0.89	84	1.00	267	0.93	96	0.99	97	–0.631	–0.454
Cancer										
Upper respiratory tract** (142, 144, 145, 147, 160, 161)	1.24	11	1.00	23	1.92	15	0.86	6	0.744	0.765
Buccal cavity (140–149)	1.98	13	1.00	25	1.59	12	1.74	12	0.422	0.365
Salivary gland (142)	NA*	0	1.00	1	3.10	1	5.98	2	0.448	0.473
Nasopharynx†† (147)	2.40	2	1.00	3	1.19	1	4.14	3	0.029	0.025
Digestive system (150–159)	0.95	97	1.00	250	0.92	84	1.08	86	–0.454	–0.457
Liver (155–156)	1.43	8	1.00	13	1.04	5	1.23	5	–0.664	–0.812
Pancreas (157)	0.70	14	1.00	53	0.67	13	0.74	13	–0.111	–0.073
Respiratory system (160–163)	0.93	110	1.00	422	0.92	136	0.82	110	–0.099	–0.076
Nose and nasal cavity (160)	NA	0	1.00	2	1.32	1	NA	0	–0.855	–0.715
Larynx (161)	0.97	6	1.00	13	1.81	9	0.23	1	–0.043	–0.027
Lung (162)	0.93	103	1.00	407	0.88	125	0.84	109	–0.165	–0.138
Bone (170)	NA	0	1.00	3	1.91	2	2.53	2	0.024	0.032
Skin (172–173)	0.21	5	1.00	20	0.41	3	1.07	6	0.926	–0.808
Breast (174)	1.45	16	1.00	14	0.90	4	0.81	1	0.892	0.616
Female genital (180–184)	1.33	16	1.00	8	1.80	4	2.67	2	0.511	0.601
Prostate (185)	0.65	14	1.00	66	0.87	26	1.31	39	0.096	0.146
Bladder (188)	1.18	6	1.00	13	1.98	10	1.73	8	–0.922	–0.846
Kidney (189)	1.38	11	1.00	22	1.39	10	0.81	5	–0.954	–0.913
Brain and central nervous system (191–192)	1.71	19	1.00	27	1.02	9	0.86	7	–0.964	0.886
Person-years	409,074		319,418		82,630		54,586			

* ICD-8, *International Classification of Diseases*, Eighth Revision; NA, not applicable (a relative risk estimate for this category of exposure was not available because there was no death in this category or in the reference category).

† Exposure was calculated by using a 15-year lag interval.

‡ Likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure for nonexposed and exposed person-years; –, negative slope estimate.

§ Likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure for exposed person-years only; –, negative slope estimate.

¶ Reference for all categories.

Relative risk from Poisson regression analysis stratified by calendar year, age (both in 5-year intervals), sex, and race (Black/White) and adjusted for pay category (salary/wage). The 95% confidence intervals for the estimated relative risks shown all included 1.00.

** Cancer of the salivary gland, floor of the mouth, other mouth, nasopharynx, nasal cavity, larynx.

†† Cause of death corrected from cancer of the nasopharynx to that of the oropharynx for one death based on information from secondary sources other than death certificates (29).

association with formaldehyde exposure was observed for pneumonia, emphysema, and all benign diseases of the respiratory system.

Sites of direct contact with formaldehyde upon inhalation include the nasopharynx, mouth, salivary gland, nasal cavity, and larynx. Cancers at these sites as a group (denoted here as upper respiratory tract) exhibited increasing relative risks with increasing average intensity and peak exposure but not with cumulative exposure and duration of exposure. Relative risks for an average exposure intensity of 0.5–<1.0

TABLE 6. Relative risks and numbers of deaths for selected cancers and other major causes of death by duration of exposure to formaldehyde, United States, mortality follow-up through 1994

Cause of death (ICD-8* code(s))	Duration of exposure (years)†								*p*-trend‡	*p*-trend§
	0		>0–<5¶		5–<15		≥15			
	Relative risk#	No. of deaths	Relative risk#	No. of deaths	Relative risk#	No. of deaths	Relative risk#	No. of deaths		
All causes (001–999)	0.96	1,991	1.00	4,007	0.95	1,391	0.94	1,097	–0.209	–0.010
All cancer (140–209)	0.92	376	1.00	1,046	0.95	372	0.92	305	–0.295	–0.092
Solid cancer (140–199)	0.94	341	1.00	961	0.94	340	0.92	279	–0.296	–0.135
Benign/unspecified neoplasms (210–239)	0.43	6	1.00	13	1.42	6	0.40	2	0.978	0.575
Circulatory system (390–458)	0.97	815	1.00	1,807	0.97	676	1.01	547	0.645	–0.809
Respiratory diseases (460–519)	0.90	84	1.00	263	1.03	101	0.91	96	–0.799	–0.385
Cancer										
Upper respiratory tract** (142, 144, 145, 147, 160, 161)	0.96	11	1.00	29	1.00	11	0.46	4	–0.206	–0.159
Buccal cavity (140–149)	1.87	13	1.00	27	1.74	16	0.95	6	0.850	0.589
Salivary gland (142)	NA*	0	1.00	1	3.29	1	5.42	2	0.213	0.243
Nasopharynx†† (147)	1.77	2	1.00	4	0.83	1	4.18	2	0.206	0.147
Digestive system (150–159)	0.96	97	1.00	247	0.98	93	1.03	80	0.832	0.848
Liver (155–156)	1.32	8	1.00	14	0.95	5	0.87	4	–0.566	–0.618
Pancreas (157)	0.70	14	1.00	52	0.69	14	0.76	13	–0.207	–0.082
Respiratory system (160–163)	0.88	110	1.00	434	0.79‡‡	129	0.77‡‡	105	–0.017	–0.008
Nose and nasal cavity (160)	NA	0	1.00	2	1.08	1	NA	0	–0.477	–0.250
Larynx (161)	0.65	6	1.00	18	0.62	5	NA	0	–0.008	–0.002
Lung (162)	0.90	103	1.00	414	0.80‡‡	123	0.80	104	–0.045	–0.028
Bone (170)	NA	0	1.00	4	1.13	2	1.27	1	0.420	0.727
Skin (172–173)	0.25	5	1.00	17	0.85	5	1.47	7	0.259	0.719
Breast (174)	1.44	16	1.00	15	0.55	2	2.03	2	0.898	0.658
Female genital (180–184)	1.11	16	1.00	10	0.83	2	2.14	2	–0.942	0.779
Prostate (185)	0.68	14	1.00	60	1.31	37	0.98	34	0.486	0.877
Bladder (188)	0.96	6	1.00	16	1.35	9	1.02	6	0.533	0.769
Kidney (189)	1.29	11	1.00	23	0.77	6	1.40	8	–0.789	–0.716
Brain and central nervous system (191–192)	1.68	19	1.00	28	1.08	10	0.61	5	–0.184	–0.368
Person-years	409,074		324,912		90,046		41,676			

* ICD-8, *International Classification of Diseases*, Eighth Revision; NA, not applicable (a relative risk estimate for this category of exposure was not available because there was no death in this category or in the reference category).

† Exposure was calculated by using a 15-year lag interval.

‡ Likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure for nonexposed and exposed person-years; –, negative slope estimate

§ Likelihood ratio test (1 df) of zero slope for continuous formaldehyde exposure for exposed person-years only; –, negative slope estimate.

¶ Reference for all categories.

Relative risk from Poisson regression analysis stratified by calendar year, age (both in 5-year intervals), sex, and race (Black/White) and adjusted for pay category (salary/wage).

** Cancer of the salivary gland, floor of the mouth, other mouth, nasopharynx, nasal cavity, larynx.

†† Cause of death corrected from cancer of the nasopharynx to that of the oropharynx for one death based on information from secondary sources other than death certificates (29).

‡‡ 95% confidence interval does not include 1.00.

and ≥1.0 versus >0–<0.5 ppm were 1.69 (95 percent confidence interval (CI): 0.80, 3.59) and 2.21 (95 percent CI: 1.10, 4.44), respectively, with a nonsignificant trend for exposed workers (p = 0.122) (table 3). Nine deaths from nasopharyngeal cancer occurred, seven among exposed and two among nonexposed workers. Four exposed cases had cumulative exposures of <5.5 ppm-years, while the other three exposed cases had cumulative exposures of 12.5, 21.7,

and 52.3 ppm-years. All exposed cases had maximum peak exposures of ≥4.0 ppm. Three deaths were added with the extended follow-up (2.5 expected), with two deaths added to the highest cumulative exposure category. Nasopharyngeal cancer mortality was elevated compared with that in the general population (SMR = 1.56 for nonexposed, SMR = 2.10 for exposed; table 2). Among the exposed, the relative risk increased with all exposure measures except duration of exposure and was two- to fourfold for workers exposed to the highest levels of formaldehyde (tables 3, 4, 5, and 6). Specifically, relative risks for 1.5–<5.5 and ≥5.5 versus >0–<1.5 ppm-years of cumulative exposure were 1.19 (95 percent CI: 0.12, 11.50) and 4.14 (95 percent CI: 0.83, 20.70), respectively, with a significant trend for exposed workers ($p = 0.025$). Three workers died from cancer of the nose or the nasal cavity. All three were exposed to formaldehyde, with cumulative exposures and peak exposures of 5.35, 0.09, and 0.13 ppm-years and ≥4.0, ≥4.0, and >0–<2.0 ppm. The standardized mortality ratio for exposed subjects was slightly elevated (SMR = 1.19; table 2), and relative risks compared with those for subjects exposed to low levels were increased for subjects exposed to higher levels of formaldehyde, even though the 95 percent confidence interval included 1.0 (tables 3, 4, 5, and 6). For salivary gland cancer (four deaths), relative risks were threefold and five- to sixfold higher for the medium- and high-exposure categories of cumulative exposure and duration of exposure, respectively, compared with low exposure. However, the confidence intervals were wide, and no association was seen for peak exposure and average intensity (tables 3, 4, 5, and 6).

Other cancer sites of a priori interest were the pancreas, prostate, and brain. Mortality from cancer of the pancreas was not associated with any of our measures of formaldehyde exposure in the total cohort (tables 3, 4, 5, and 6). Relative risks increased with average exposure intensity only for the subgroup of older subjects (aged ≥65 years), but the trend was not statistically significant (table 7). For prostate cancer, a significantly elevated relative risk of 1.61 (95 percent CI: 1.04, 2.47) occurred for workers with peak formaldehyde exposure of 2.0–<4.0 ppm (42 deaths), but the trend with peak exposure was not statistically significant (table 4). Relative risks for categories of average exposure intensity were slightly elevated, and the trend was borderline significant ($p = 0.065$) for exposed subjects (table 3) and significant or borderline significant for the subgroups of White workers ($p = 0.053$), older workers (aged ≥65 years, $p = 0.086$), wage workers ($p = 0.067$), and workers never exposed to formaldehyde-containing particulates ($p = 0.021$) (table 7). No association was observed for mortality from malignant brain tumors (62 deaths) (tables 3, 4, 5, and 6).

Some associations were observed for cancers not of a priori interest. There were seven deaths from bone cancer among exposed workers (SMR = 1.57 among exposed) and none among nonexposed workers (2.9 expected). Relative risks increased with exposure, particularly for cumulative exposure. The relative risks for workers exposed for 1.5–<5.5 and ≥5.5 ppm-years were 1.91 (95 percent CI: 0.31, 11.64) and 2.53 (95 percent CI: 0.40, 16.03), respectively, compared with workers exposed to low levels (>0–<1.5 ppm-years) of formaldehyde, with a significant trend for exposed workers ($p = 0.032$) (table 5). For liver cancer (31 deaths), we found an association with peak exposure. When we compared workers exposed to peak levels of 2.0–<4.0 ppm and ≥4.0 ppm with workers exposed to low peak levels of formaldehyde (>0–<2.0 ppm), the relative risks were 1.54 (95 percent CI: 0.50, 4.73) and 2.18 (95 percent CI: 0.80, 5.99), respectively, with a significant trend for exposed workers ($p = 0.045$) (table 4). However, no association was observed for other exposure measures (tables 3, 5, and 6).

Exposure to substances other than formaldehyde

Forty-seven percent of the subjects were ever occupationally exposed to at least one of the following substances: antioxidants (22 percent), asbestos (14 percent), carbon black (11 percent), dyes and pigments (16 percent), hexamethylenetetramine (15 percent), melamine (28 percent), phenol (14 percent), plasticizers (20 percent), urea (27 percent), wood dust (10 percent), and benzene (2 percent). Relative risks for various cancers and formaldehyde exposure categories did not change substantially when adjusted for duration of exposure to these substances, except for nasopharyngeal cancer and melamine exposure. For that site, relative risks for the highest exposure categories of peak and average intensity of formaldehyde exposure declined when the analysis was adjusted for melamine exposure (data not shown). However, relative risks were still elevated for cumulative exposure and duration of exposure after adjustment for melamine exposure, and trend tests remained significant for peak ($p < 0.001$), average ($p = 0.021$), and cumulative ($p = 0.006$) exposure. We repeated the analyses for all cancers of interest by excluding the 586 subjects exposed to benzene and found no substantial differences. Only 8 percent of all workers were employed as chemists or laboratory technicians, and only 2 percent worked in such jobs for 5 or more years. Adjusting for duration of working as a chemist or laboratory technician did not substantially change the observed associations.

DISCUSSION

When the follow-up was extended, we found no evidence that lung cancer is associated with formaldehyde exposure. This finding is consistent with results based on the initial follow-up (5, 28, 34), where workers exposed to formaldehyde had slight excesses of mortality from lung cancer, but these excesses were not consistently related to duration of or average, cumulative, or peak formaldehyde exposure levels. Other investigators reanalyzed our original data from the initial follow-up and interpreted elevated risks for exposed subjects compared with nonexposed subjects as evidence for a causal relation (35–37), or they found an association between lung cancer mortality and cumulative exposure to formaldehyde only in the presence of several coexposures (38).

Risk estimates for lung cancer from formaldehyde exposure could have been confounded by other occupational exposures and smoking. Confounding from exposure to 11 other substances is less likely since there was no evidence of an association between lung cancer mortality and these

TABLE 7. Effect modification of average formaldehyde intensity for selected cancer sites, United States, mortality follow-up through 1994

Effect modifier	Average intensity*								*p*-trend†	*p*-heterogeneity‡
	0		>0–<0.5§		0.5–<1		≥1			
	Relative risk¶	No. of deaths	Relative risk¶	No. of deaths	Relative risk¶	No. of deaths	Relative risk¶	No. of deaths		
Pancreas (157#)										
Age (years)										
<50	0.89	3	1.00	3	0.94	1	0.96	1	–0.729	
≥50–<65	0.66	6	1.00	24	0.12	1	0.67	6	–0.214	
≥65	0.85	5	1.00	21	1.38	10	1.49	12	0.423	0.315
Pay category										
Wage	0.78	10	1.00	38	0.63	9	1.11	19	0.975	
Salary	0.33	2	1.00	9	1.17	3	NA††	0	–0.411	0.416
Exposure to formaldehyde-containing particulates										
Never	0.72	14	1.00	20	0.64	4	1.34	5	0.301	
Ever	NA	0	1.00	28	0.78	8	1.02	14	–0.320	0.149
Lung (162#)										
Age (years)										
<50	1.17	14	1.00	22	1.64	11	0.76	5	–0.516	
≥50–<65	0.91	51	1.00	173	1.12	69	0.95	64	–0.296	
≥65	1.16	38	1.00	153	1.12	61	1.39**	83	0.148	0.164
Pay category										
Wage	1.02	67	1.00	293	1.12	125	1.12	145	0.978	
Salary	0.99	28	1.00	44	1.19	15	1.62	7	0.352	0.362
Exposure to formaldehyde-containing particulates										
Never	0.91	98	1.00	145	1.16	55	0.81	22	–0.262	
Ever	1.17	5	1.00	203	1.15	86	1.30**	130	0.218	0.101

Table continues

exposures, and adjusting the analysis for duration of exposure to these 11 substances did not change the results. We lacked information on tobacco use for most of the cohort, but evidence suggests that smoking is not a confounder since there was no consistent excess or deficit for other tobacco-related diseases, for example, bladder cancer, emphysema, and ischemic heart disease. Information on smoking habits obtained from medical records for a small sample of workers from two plants (63 subjects with cancer and 316 age-matched controls) revealed no major differences in smoking prevalence by level of cumulative formaldehyde exposure (28). Pay category, which correlates with socioeconomic status and smoking prevalence, was included as an adjustment factor in the analysis. Our null finding for formaldehyde exposure and lung cancer is consistent with several recent studies (26, 39–41), although other studies of industrial populations have suggested increased lung cancer mortality (16–18).

The factor plant was taken into account in our analysis. We directly addressed potential confounding by plant-related factors by adjusting for 11 potentially confounding substances. Directly adjusting for plant may result in overadjustment. However, to address the potential effect of unmeasured confounders associated with plant, we performed analyses adjusted for plant. Although some of these analyses were based on small numbers, and, as a consequence, estimates had large variances, associations observed for cancers of the upper respiratory tract, nasopharynx, salivary gland, nose or nasal cavity, and bone remained after we adjusted for plant. In the adjusted analysis, no clear association was seen for cancers of the pancreas, brain, lung, or prostate.

Inhaled formaldehyde is deposited almost entirely in the upper respiratory tract of rats (42) and is rapidly incorporated into DNA, RNA, and proteins (43). Therefore, the upper respiratory tract is the site of direct exposure for inhaled formaldehyde. Despite the small numbers of deaths from cancers of the upper respiratory tract, the positive association for this site as a group with average intensity and peak exposure in our analysis is consistent with the carcinogenicity of formaldehyde at the site of first contact. Several epidemiologic (7–12, 14, 24, 44) and animal (3, 4) studies support these results for specific sites in the upper respira-

TABLE 7. Continued

Effect modifier	Average intensity*								*p*-trend†	*p*-heterogeneity‡
	0		>0–<0.5§		0.5–<1		≥1			
	Relative risk¶	No. of deaths	Relative risk¶	No. of deaths	Relative risk¶	No. of deaths	Relative risk¶	No. of deaths		
Prostate (185#)										
Race										
White	0.80	13	1.00	61	1.24	26	1.24	26	0.053	
Black	0.04	1	1.00	11	1.41	5	0.69	2	–0.861	0.541
Age (years)										
<50	0.11	1	1.00	1	NA	0	NA	0	–0.366	
≥50–<65	1.19	3	1.00	9	0.70	2	1.32	4	0.389	
≥65	0.62	10	1.00	62	1.36	29	1.18	24	0.086	0.580
Pay category										
Wage	0.61	7	1.00	52	1.31	26	1.17	26	0.067	
Salary	0.69	6	1.00	16	1.07	5	1.51	2	0.697	0.975
Exposure to formaldehyde-containing particulates										
Never	0.72	13	1.00	24	1.35	9	1.51	6	0.021	
Ever	0.54	1	1.00	48	1.22	22	1.09	22	0.616	0.133
Brain and central nervous system (191–192#)										
Age (years)										
<50	0.53	8	1.00	3	1.93	2	2.54	3	0.717	
≥50–<65	4.84	9	1.00	10	1.35	5	0.99	4	0.935	
≥65	1.23	2	1.00	10	0.54	2	0.93	4	0.659	0.950
Pay category										
Wage	2.00	15	1.00	19	1.26	9	1.31	11	0.621	
Salary	1.23	4	1.00	4	NA	0	NA	0	–0.956	0.896
Exposure to formaldehyde-containing particulates										
Never	2.02	18	1.00	7	0.86	2	1.52	2	0.229	
Ever	9.80**	1	1.00	16	1.14	7	1.07	9	–0.828	0.267

* Exposure was calculated by using a 15-year lag interval.

† Likelihood ratio test of zero slope for continuous formaldehyde intensity for exposed person-years only; –, negative slope estimate.

‡ Likelihood ratio test of heterogeneity of relative risks for intensity between levels of the effect modifier.

§ Reference for all categories.

¶ Relative risk from Poisson regression analysis stratified by calendar year, age (both in 5-year intervals), sex, and race (Black/White) and adjusted for pay category (salary/wage).

International Classification of Diseases, Eighth Revision code(s).

** 95% confidence interval does not include 1.00.

†† NA, not applicable (a relative risk estimate for this category of exposure was not available because there was no death in this category or in the reference category).

tory tract, while other studies (16, 20, 26, 39, 45–47) provide little support.

Some cohort studies (10), including ours, and some case-control studies (9, 11–14) reported a positive association between formaldehyde exposure and nasopharyngeal cancer, whereas others (16, 20, 26, 39, 45–47) did not. One study found a positive association for hypopharyngeal cancer (48). The excess for nasopharyngeal cancer reported previously in this cohort persisted, although only three additional deaths occurred in the extended follow-up. We observed exposure-response patterns for nasopharyngeal cancer for average, cumulative, and peak exposure to formaldehyde. Because five of the nine deaths from nasopharyngeal cancer occurred at one plant (plant 1; table 1), we performed analyses adjusted for plant and found increasing relative risks with increasing exposure categories for all four exposure metrics. Specifically, adjusted relative risks for the categories shown in tables 3, 4, 5, and 6 were, respectively, 1.00, (not applicable), (not applicable), and 9.07 for peak exposure (*p*-trend among exposed = 0.008); 1.00, (not applicable), 8.51, and 23.54 for average intensity (*p*-trend among exposed = 0.404); 2.18, 1.00, 1.34, and 5.32 for cumulative exposure

(p-trend among exposed = 0.007); and 1.76, 1.00, 1.21, and 8.59 for duration of exposure (p-trend among exposed = 0.043). These results are consistent with increasing standardized mortality ratios with increasing cumulative exposure and duration of exposure to formaldehyde found in an independent investigation of workers at this plant (including all workers hired between 1941 and 1984 and followed through 1998) (49).

Of the nine workers who died from nasopharyngeal cancer, two were not exposed to formaldehyde and were never exposed to particulates, whereas seven workers were exposed to formaldehyde and to particulates. This complete colinearity of exposure to formaldehyde and particulates prevented us from evaluating formaldehyde exposure separately for those workers exposed and not exposed to particulates. However, nasopharyngeal cancer risk increased with formaldehyde exposure for those exposed to particulates, and formaldehyde intensities and peak exposures ranged from low to high in the jobs involving and not involving particulate exposure held by the nine workers who died from nasopharyngeal cancer. This finding provides evidence that the association seen for formaldehyde may not be entirely due to particulates.

Workers could contribute person-time and deaths to high peak exposure categories based on infrequent peaks because peaks may have occurred in jobs of short duration or occurred less often than daily or weekly, or both. We created several alternative maximum peak exposure metrics, ignoring peaks in jobs of short duration (<6 or <12 months) or rare peaks (less often than daily or weekly), and found two- to sevenfold increased risks for nasopharyngeal cancer in the highest peak exposure category (≥4.0 ppm) compared with the nonexposed category.

Wood dust is a potential confounder for formaldehyde exposure and nasal and nasopharyngeal cancer (2, 47, 50); however, none of our nasal and nasopharyngeal cancer cases had been identified as being exposed to wood dust. For nasopharyngeal cancer, some confounding was observed by duration of exposure to melamine. Exposure to melamine occurred at six plants, mainly in the manufacture of synthetic resins with formaldehyde. Although exposure to high doses of melamine produced urinary bladder and ureteral carcinomas in rats, there is inadequate evidence for the carcinogenicity of melamine in humans (51). Therefore, the observed association between melamine exposure and nasopharyngeal cancer and subsequent confounding of the formaldehyde-nasopharyngeal cancer association may be spurious. No information was available on the presence of antibodies to Epstein-Barr virus, another major risk factor for nasopharyngeal cancer (52).

Inhaled formaldehyde causes nasal cavity tumors in mice (3), and some epidemiologic studies have reported a positive association between formaldehyde exposure and cancer of the nasal cavity (44, 53, 54). A meta-analysis found an increased risk in 11 case-control studies but not in nine cohort studies of industrial workers (39), although many of the studies that did not show an association had generally low power because of small numbers of cases, uncertainties in the exposure assessment, or both. The association for cancer of the nasal cavity found in the current analysis is consistent with an effect, but the number of deaths was too limited to enable a firm conclusion.

In a cohort of workers exposed to formaldehyde in the garment industry, Stayner et al. (55) found a significant excess of cancer of the buccal cavity (3 observed, 0.4 expected), with the three observed deaths attributed to cancer of the parotid gland, which is part of the salivary gland. Although our numbers were also small regarding cancer of the salivary gland (four deaths), we did see increasing relative risks with categories of cumulative exposure and duration of exposure. This finding is consistent with recent data from a death-certificate-based case-control study including 2,405 salivary gland cancer deaths and showing an increased risk with occupational exposure to formaldehyde (56).

Our finding of no association between formaldehyde exposure and pancreatic cancer is consistent with a recent review and meta-analysis of 14 studies; no elevated risk was found for industrial workers, although a slightly elevated risk was found for embalmers, pathologists, and anatomists (19).

The association between formaldehyde exposure and prostate cancer has been mixed, with weakly positive associations (10, 15), no associations (16, 20, 21), and protective effects (24, 45) reported. In the initial report on this cohort (5), a slight excess was confined largely to salaried workers, suggesting that the association was due to socioeconomic factors rather than occupational exposures. The moderate positive association between formaldehyde exposure and prostate cancer observed in the current analysis, especially for wage workers and older workers, is suggestive, but the absence of a clear exposure-response gradient and internal inconsistencies among wage and salaried workers do not provide much evidence for a causal relation.

Most studies of embalmers or pathologists have reported nonsignificantly elevated standardized mortality ratios for brain cancer (10, 15, 20–22). One study of anatomists found significantly elevated standardized mortality ratios that increased with duration of membership in the anatomists' association (23). For industrial workers, no association (6, 16, 26, 45, 46) or small excesses (24) have been reported. The previous analysis of this cohort (5) found no link between brain cancer and formaldehyde exposure, and we found no association after the extended follow-up.

The excess mortality from bone cancer is interesting, but, to our knowledge, this site has not been linked with formaldehyde exposure in previous experimental or epidemiologic investigations. Interpretation of the finding is problematic because of the small number of deaths (n = 7) and because the bone is a common site of metastases. However, the size of the relative risk and occurrence among only the exposed suggest that further consideration is warranted. As far as we know, liver cancer has not been linked to formaldehyde exposure, and the observed association may be a chance finding.

Our study has limitations. Extension of mortality follow-up from 1980 through 1994 utilized only the National Death Index Plus to determine vital status. Subjects not identified as deceased by this source were assumed to be alive. Although the National Death Index Plus is quite complete, it

is possible that there was some underascertainment of deaths. However, it is unlikely that this factor would bias relative risk estimates because missing deaths are unlikely to be related to formaldehyde exposure. Exposure misclassification is always a concern in epidemiologic investigations. The detailed quantitative assessment of time-weighted average exposure intensity in this study used monitoring data provided by the companies, monitoring in each plant by study investigators (33), visits to the plants by study industrial hygienists, and discussions with plant managers and long-time workers (30). Therefore, this process should minimize misclassification for average and cumulative exposure and duration of exposure. Assessment of peak exposure could have been more susceptible to misclassification since peak levels were estimated from job tasks and the time-weighted average exposure. However, since any misclassification of formaldehyde exposure most likely was nondifferential, the potential effect would be an attenuation of risk estimates. Therefore, exposure misclassification could explain a lack of association, but the exposure assessment procedure was sufficient to yield an exposure-response relation with nasopharyngeal cancer and leukemia (27), lending support to the null findings for lung cancer and other a priori sites.

The study also has a number of strengths. Follow-up was as long as 60 years, and there was extensive information on formaldehyde exposure. The long follow-up yielded 8,486 deaths, which provided adequate power to detect relatively small effects for common cancer sites. We had at least 80 percent power to detect a 1.3-fold lung cancer relative risk for workers exposed to high versus low levels of formaldehyde for cumulative exposure, peak exposure, and average intensity. We were able to assess formaldehyde exposure according to several measures that characterize different aspects of exposure, thereby diminishing the chances that a true association was missed because an inappropriate exposure metric was chosen. Biases from exposure misclassification, confounding, or other factors may have influenced results for one exposure measure but are less likely to have affected all measures equally (57), thus allowing for a more robust interpretation of the data. We were able to control for possible confounding from a number of other workplace chemicals. Availability of information on tobacco use for a small subset of workers indicates that smoking was not related to formaldehyde exposure and thus should not have been a confounder. In addition, we did not rely on external comparisons (SMRs), which are subject to a healthy worker bias (58), but instead focused on internal analyses comparing similar subjects.

In summary, analysis of this cohort of workers in the formaldehyde industry, which included additional years of follow-up, supports a possible causal association with mortality from cancer of the nasopharynx and possibly other upper respiratory tract sites. The association with prostate cancer could be a chance finding since there was no exposure-response gradient. Because bone is a common metastatic site, the observed excess of bone cancer is difficult to interpret. No association was seen with cancers of the pancreas, the brain, or the lung.

ACKNOWLEDGMENTS

The authors thank Dr. Robert Hoover for his review and helpful suggestions. They shared the manuscript with participating companies and unions and appreciate their comments.

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