Mortality From Lymphohematopoietic Malignancies Among Workers in Formaldehyde Industries

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Background: **Many U.S. factory workers are exposed to formaldehyde. Although increased risks for leukemia have been found in medical workers and other professionals exposed to formaldehyde, studies in industrial workers, who are thought to have higher exposures, have shown inconsistent associations. We extended follow-up of a cohort of industrial workers to evaluate the association between formaldehyde exposure and lymphohematopoietic cancers.** ***Methods:*** **The cohort consisted of 25 619 workers (865 708 person-years) employed before January 1, 1966, at one of 10 U.S. industrial plants and followed through December 31, 1994. We analyzed formaldehyde exposure (peak exposure, average exposure intensity, cumulative exposure, and duration of exposure) and mortality from lymphohematopoietic malignancies using standardized mortality ratios and relative risks and 95% confidence intervals (CIs) based on Poisson regression. Statistical tests were two-sided.** ***Results:*** **Among the cohort, there were 178 deaths from lymphohematopoietic malignancies. Relative risks for leukemia (69 deaths), particularly for myeloid leukemia (30 deaths), increased with formaldehyde exposure. Compared with workers exposed to low peak levels of formaldehyde (0.1–1.9 ppm), relative risks for myeloid leukemia were 2.43 (95% CI = 0.81 to 7.25) and 3.46 (95% CI = 1.27 to 9.43) for workers exposed to peak levels of 2.0–3.9 ppm and ≥4.0 ppm, respectively (P_{trend} = .009). Compared with workers exposed to low levels of average exposure intensity of formaldehyde (0.1–0.4 ppm), workers exposed to 0.5–0.9 ppm and ≥1.0 ppm average intensity had relative risks of 1.15 (95% CI = 0.41 to 3.23) and 2.49 (95% CI = 1.03 to 6.03), respectively (P_{trend} = .088). The relative risk for leukemia was not associated with cumulative exposure but was weakly associated with duration of exposure. Relative risks for Hodgkin's disease also increased with formaldehyde exposure.** ***Conclusions:*** **Exposure to formaldehyde may cause leukemia, particularly myeloid leukemia, in humans. However, results from other investigations are mixed, suggesting caution in drawing definitive conclusions. [J Natl Cancer Inst 2003;95: 1615–23]**

Approximately 12 million tons of formaldehyde, a flammable and colorless gas, were produced worldwide in 1992 *(1)*. Formaldehyde is used in the production of resins, molding compounds, photographic film, decorative laminates, and plywood, and as a bactericide and a tissue preservative. The U.S. National Institute of Occupational Safety and Health estimated that, in 1981–1983, approximately 1.5 million workers in the United States were exposed to formaldehyde *(2)*. Occupational exposures occur mainly to formaldehyde gas. However, formaldehyde-containing particulates can occur as products (i.e., paraform) or can be formed when formaldehyde gas adheres to

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carrier agents such as wood dust. Dermal exposure is possible from formalin solutions or liquid resins *(3)*.

Formaldehyde at a concentration of approximately 0.5–1 ppm causes acute health effects, including irritation of the eye and upper airway mucosa *(3)*. Rats and mice that were exposed by inhalation to formaldehyde gas at concentrations of greater than 5 ppm for 2 or more years developed squamous cell carcinomas of the nasal cavity *(4,5)*. However, formaldehyde can have effects away from the site of exposure. Human leukocytes exposed to formaldehyde developed DNA–protein cross-links *in vitro* and *in vivo*, which may result in a loss of genetic material *(6)*.

The International Agency for Research on Cancer found sufficient evidence to declare that formaldehyde is carcinogenic in animals but only limited evidence for carcinogenicity in humans *(3)*. However, formaldehyde exposure has been associated with cancer of the nasal sinuses and nasopharynx in some studies of industrial workers *(3)*. Although some studies have reported an increased risk of leukemia (range of standardized mortality ratios [SMRs] = 1.1–3.0) among medical workers and other professionals exposed to formaldehyde, the results of studies among industrial workers are mixed *(3)*. We previously assessed mortality among the largest cohort of industrial workers exposed to formaldehyde *(7)*. Here, we extended follow-up of the cohort by 15 years, and assessed the relationship between formaldehyde exposure and lymphohematopoietic malignancies.

Subjects and Methods

Cohort Design and Follow-up

Details of the study design have been described previously *(7,8)*. In brief, the cohort consisted of 25 619 workers first employed at one of 10 industrial plants before January 1, 1966 (878 workers of unknown sex or race/ethnicity and 64 workers who started work after January 1, 1966, were excluded). In the original follow-up *(7)*, information for each worker regarding birth date, race/ethnicity, sex, and each job held at a participating plant was obtained from company records. Subjects were followed from the year of initial cohort identification (1934–1958, depending on the plant) or first employment at a plant, whichever was later, through January 1, 1980. Data from the Social Security Administration, Health Care Finance Administration, Veterans Administration, credit bureaus, motor vehicle departments, and telephone directories were used to determine vital status. Death certificates were obtained for 4349 individuals through 1980 to determine the underlying cause of death. For the 866 subjects (3.4%) lost to follow-up, follow-up ended at the last date known alive.

In this study, we extended the mortality follow-up through December 31, 1994. All subjects alive on January 1, 1980, were linked to the National Death Index Plus (http://www.cdc.gov/nchs/r&d/ndi/ndi.htm). For deceased individuals, information was collected from death certificates to establish the underlying cause of death. A total of 4137 new deaths were identified. The total number of deaths for the cohort was therefore 8486. The remaining subjects were assumed to be alive on December 31, 1994.

During this study, we did not contact study participants. Therefore, the institutional review board of the National Institutes of Health (Bethesda, MD) determined that the study was exempt from review. Approval was obtained from state institutional review boards, where necessary, to obtain death certificates.

Exposure Assessment

The 10 industrial plants included in this study produced formaldehyde (three plants), formaldehyde resins (six plants), molding compounds (six plants), molded plastic products (two plants), photographic film (two plants), and plywood (one plant). Exposure to formaldehyde was estimated from work histories collected through 1980 on the basis of 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 exposures (generally <15 minutes) that exceeded the 8-hour, time-weighted average formaldehyde exposure intensity. Peak exposures in the workplace occurred from routine (i.e., hourly, daily, or weekly) or nonroutine high-exposure tasks or from working in areas where nonroutine unusual upsets or events, such as spills, occur. No measurements of peak exposure were available in this study. Peak exposures were therefore estimated by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-weighted average. The presence of particulates (i.e., solid formaldehyde such as paraform or trioxane), a formaldehyde-containing resin or molding compound particulate, or a particulate onto which formaldehyde gas could be adsorbed, was assessed. The routine use of respirators was determined. We identified exposures to 11 other widely used chemicals in the plants (i.e., 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. A comprehensive description of the exposure assessment is given elsewhere *(7,9,10)*. No information on formaldehyde exposure after 1980 was available.

Statistical Analysis

Subjects contributed person-years from the time of entry into the cohort (1934–1966) through time of death or December 31, 1994, whichever was earlier. For each job, the following was available: 8-hour time-weighted average formaldehyde exposure intensity (in ppm), peak formaldehyde exposure category (unexposed, 0.1–1.9 ppm, 2.0–3.9 ppm, ≥4 ppm), frequency of peak exposure (none, hourly, daily, weekly, monthly), presence of particulates (yes/no), routine respirator use (yes/no), exposure to each of 11 other substances (yes/no), and working as a chemist or laboratory technician (yes/no). On the basis of this information, the following exposure variables were calculated as time-dependent variables: cumulative formaldehyde exposure (in ppm-years), average formaldehyde exposure intensity (in ppm), and highest peak formaldehyde exposure category. In addition, we calculated duration of formaldehyde exposure (in years) because this measure is widely used in occupational epidemiologic studies. However, the validity of exposure duration requires the assumption that the exposure rate for all jobs and over time be constant, which was not true in this, and most similar, situations. We also calculated exposure to formaldehyde-containing particulates (ever/never), duration of exposure to each of 11 other substances (in years), and duration of working as a chemist or laboratory technician (in years). Cut points for formaldehyde exposure categories were approximately the 60th and 80th percentiles of the distribution of the respective exposure measure in exposed subjects who died from cancer. These cut points ensured that there were sufficient numbers of case subjects in the exposed categories.

SMRs were calculated using sex-, race-/ethnicity-, age-, and calendar year–specific U.S. mortality rates. For internal analy-

ses, relative risks and 95% confidence intervals (CIs) were estimated using log-linear Poisson regression models *(11)* stratified by calendar year (1930–1934, 1935–1939, . . . , 1990–1994), age (0–14, 15–19, . . . , 75–79, 80+), sex, and race/ethnicity (black/white) and adjusted for pay category (annual salary/hourly wage/unknown). The low-exposure categories (i.e., 0.1–1.9 ppm for peak exposure, 0.1–0.4 ppm for average exposure intensity, 0.1–1.4 ppm-years for cumulative exposure, and 0.1–4.9 years for duration of exposure) were used as the reference categories to minimize the impact of any unmeasured confounding variables because unexposed workers may have differed from exposed workers with respect to socioeconomic characteristics. However, workers in the low-exposure categories were exposed to very low levels of formaldehyde and are thus an appropriate referent group. Potential confounding was evaluated for exposure to 11 other substances (listed above) and for working as a chemist or laboratory technician. Tests of trend for categorical variables were based on the likelihood ratio for the slope of the corresponding continuous variable, with the exception of peak exposure, for which categorical ranks were used. Heterogeneity among risk estimates was assessed by likelihood ratio tests. Tests were two-sided at a 5% significance level. EPICURE software *(12)* was used for the analysis.

All exposures were calculated using a 2-year lag interval to account for latency, i.e., for the fact that formaldehyde exposures received within 2 years before death are unlikely to be associated with the cause of death. We evaluated various lag intervals from 2 to 20 years and did not find substantial differences in goodness of model fit from the 2-year lag interval (data not shown).

Relative risk estimates were not adjusted for plant because plant is highly correlated with exposure. However, we repeated the analyses, selectively omitting one plant at a time, and found relative risk estimates to be similar to those from the analysis that included all plants (data not shown).

Results

Demographic Description of the Cohort

The cohort included 25 619 subjects, 75% of whom entered the cohort before 1960, and 865 708 person-years. The duration of follow-up ranged from a few days to 58 years, with a median duration of 35 years. Median ages at entry and end of follow-up were 26 and 64 years, respectively. The majority of the cohort were white men (81%) (Table 1). Less than 20% of the cohort consisted of white women (12%), black men (7%), or black women (<1%) (Table 1).

Exposure to Formaldehyde

The median time-weighted average formaldehyde exposure intensity for workers in jobs exposed to formaldehyde was 0.5 ppm (range = 0.0–4.3 ppm), and 17% of all jobs and 3201 individuals had no exposure to formaldehyde. Of all jobs, 2.6% had average exposure intensities of 2 ppm or higher, and 14.3% had peak exposures of 4 ppm or higher. These exposures were generally similar to or slightly higher than those in other studies examining occupational exposures to formaldehyde *(13)*. The median duration in jobs with exposure to formaldehyde was 2 years (range = 1 day to 46 years). Cumulative exposure to formaldehyde ranged from zero to 107 ppm-years. Approximately 0.5% (n = 133) of the individuals in the cohort ever routinely used a respirator and, of these, only 24 individuals used one routinely for 5 or more years.

Table 1. Demographic characteristics of the cohort*

Demographic characteristic	No. of subjects (%)	Person-years (%)
Ethnicity and sex		
Men		
White	20 658 (81)	702 371 (81)
Black	1835 (7)	56 467 (7)
Women		
White	3100 (12)	106 065 (12)
Black	26 (<1)	805 (<1)
Year of entry into cohort		
Before 1945	3105 (12)	118 398 (14)
1946–1955	11 200 (44)	399 384 (46)
1956–1965	11 314 (44)	347 927 (40)
Age at entry, y		
≤30	16 877 (66)	601 727 (70)
31–40	5122 (20)	170 793 (20)
41–50	2593 (10)	72 557 (8)
51–60	838 (3)	18 055 (2)
≥61	189 (1)	2577 (<1)
Duration of follow-up, y		
≤30	8273 (32)	172 723 (20)
31–35	5092 (20)	169 630 (20)
36–40	5109 (20)	195 628 (23)
≥41	7145 (28)	327 727 (38)
Vital status		
Alive	16 267 (64)	633 576 (73)
Deceased	8486 (33)	228 050 (26)
Unknown	866 (3)	4081 (<1)
Total	25 619 (100)	865 708 (100)

*Percentages may not add up to 100 due to rounding.

Formaldehyde Exposure and Mortality

Among the 2099 cancer deaths in the cohort, there were 178 deaths from lymphohematopoietic malignancies: 17 among unexposed workers, and 161 among exposed workers (Table 2). Compared with mortality among the U.S. population, mortality from all causes, all cancers, and all lymphohematopoietic malignancies was statistically significantly lower among workers, regardless of exposure status. For unexposed workers, the SMRs for mortality from all causes, all cancers, and all lymphohematopoietic malignancies were 0.77 (95% CI = 0.72 to 0.83), 0.65 (95% CI = 0.56 to 0.75), and 0.62 (95% CI = 0.39 to 1.00), respectively. For exposed workers, the SMRs for mortality from all causes, all cancers, and all lymphohematopoietic malignancies were 0.95 (95% CI = 0.93 to 0.97), 0.90 (95% CI = 0.86 to 0.94), and 0.80 (95% CI = 0.69 to 0.94), respectively. In exposed workers, there were statistically significantly fewer deaths than expected from non-Hodgkin's lymphoma (SMR = 0.61, 95% CI = 0.46 to 0.83), whereas there were more deaths than expected from Hodgkin's disease (SMR = 1.26, 95% CI = 0.81 to 1.95), although the increase was not statistically significant. Among unexposed workers, there were statistically significantly fewer deaths than expected from leukemia (SMR = 0.38, 95% CI = 0.14 to 1.00) and more deaths than expected from multiple myeloma (SMR = 1.23, 95% CI = 0.51 to 2.95), although the increase was not statistically significant.

The relative risks for leukemia (69 deaths) increased by peak and average level of exposure to formaldehyde, particularly for myeloid leukemia (30 deaths). Compared with workers exposed

Table 2. Number of observed deaths and standardized mortality ratios (SMRs) with 95% confidence intervals (CIs)*

Cause of death (ICD codes†)	No. of observed deaths		SMR (95% CI)	
	Unexposed	Exposed	Unexposed	Exposed
All causes (001–999)	827	7659	0.77 (0.72 to 0.83)	0.95 (0.93 to 0.97
All cancer (140–209)	183	1916	0.65 (0.56 to 0.75)	0.90 (0.86 to 0.94
All solid malignant neoplasms (140–199)	166	1755	0.65 (0.56 to 0.76)	0.91 (0.87 to 0.96
Lymphohematopoietic malignancies (200–209)	17	161	0.62 (0.39 to 1.00)	0.80 (0.69 to 0.94
Non-Hodgkin's lymphoma (200, 202)	5	44	0.52 (0.22 to 1.25)	0.61 (0.46 to 0.83
Hodgkin's disease (201)	1	20	0.37 (0.05 to 2.65)	1.26 (0.81 to 1.95
Multiple myeloma (203)	5	28	1.23 (0.51 to 2.95)	0.88 (0.61 to 1.28
Leukemia (204–207)	4	65	0.38 (0.14 to 1.00)	0.85 (0.67 to 1.09
Benign neoplasms (210–239)	1	26	0.26 (0.04 to 1.87)	1.12 (0.76 to 1.64
Circulatory system diseases (390–458)	371	3474	0.68 (0.62 to 0.76)	0.88 (0.85 to 0.91
Respiratory diseases (460–519)	43	501	0.50 (0.37 to 0.67)	0.81 (0.74 to 0.89
No. of person-years	135 396	730 312		

*Exposure status was calculated by using a 2-year lag interval.

†Codes of the International Classification of Diseases (ICD), 8th revision.

Table 3. Relative risks for mortality from lymphohematopoietic malignancies by peak exposure to formaldehyde*

Cause of death (ICD†)	Relative risk (95% confidence interval)‡ No. of deaths				P_{trend}§	P_{trend}
	Peak exposure, ppm¶					
	0	0.1–1.9	2.0–3.9	≥4.0		
Lymphohematopoietic malignancies (200–209)	1.08 (0.60 to 1.94) 17	1.00 (Referent) 48	1.71 (1.14 to 2.58) 49	1.87 (1.27 to 2.75) 64	.002	.002
Non-Hodgkin's lymphoma (200, 202)	1.12 (0.38 to 3.31) 5	1.00 (Referent) 15	1.39 (0.67 to 2.91) 14	1.23 (0.59 to 2.55) 15	.604	.536
Hodgkin's disease (201)	0.51 (0.06 to 4.52) 1	1.00 (Referent) 5	3.45 (0.98 to 12.16) 7	3.35 (0.97 to 11.59) 8	.014	.042
Multiple myeloma (203)	2.10 (0.66 to 6.75) 5	1.00 (Referent) 9	1.48 (0.56 to 3.92) 8	1.67 (0.68 to 4.12) 11	.669	.355
Leukemia (204–207)	0.78 (0.25 to 2.43) 4	1.00 (Referent) 16	2.04 (1.04 to 4.01) 20	2.46 (1.31 to 4.62) 29	.001	.004
Lymphatic leukemia (204)	0.00 (0.00 to 2.24) 0	1.00 (Referent) 6	1.51 (0.48 to 4.74) 6	1.39 (0.46 to 4.17) 7	.279	.559
Myeloid leukemia (205)	0.67 (0.12 to 3.61) 2	1.00 (Referent) 6	2.43 (0.81 to 7.25) 8	3.46 (1.27 to 9.43) 14	.003	.009
Other/unspecified leukemia (207)	1.92 (0.33 to 11.33) 2	1.00 (Referent) 4	2.33 (0.63 to 8.66) 6	2.47 (0.69 to 8.87) 7	.277	.154
No. of person-years	135 396	335 923	194 468	199 921		

*Analyses were not feasible for polycythemia vera (ICD 208, one death) and myelofibrosis (ICD 209, five deaths) due to small numbers. No association wit formaldehyde exposure was observed for other diseases of blood cells in the bone marrow, including seven deaths from anemia of which four were aplastic, on was hypochromic with iron loading, one was specified as other, and one was unspecified, and three deaths from agranulocytosis.

†Codes of the International Classification of Diseases (ICD), 8th revision.

‡Relative risks were derived from Poisson regression stratified for calendar year, age (both in 5-year intervals), sex, and race/ethnicity (black/white), and adjuste for pay category (salary/wage). Cut points for formaldehyde exposure categories were approximately the 60th and 80th percentiles of the distribution of the respectiv exposure measure in exposed subjects who died from cancer. These cut points ensured that there were sufficient numbers of cases in the exposed categories.

§Two-sided likelihood ratio test (1 degree of freedom) of zero slope for continuous formaldehyde exposure among unexposed and exposed person-years parentheses indicate negative slope estimate.

‖Two-sided likelihood ratio test (1 degree of freedom) of zero slope for continuous formaldehyde exposure among exposed person-years only; parentheses indicat negative slope estimate.

¶Exposure was calculated using a 2-year lag interval.

to low levels of formaldehyde (0.1–1.9 ppm peak exposure or 0.1–0.4 ppm average exposure intensity), relative risks for myeloid leukemia were 2.43 (95% CI = 0.81 to 7.25) and 3.46 (95% CI = 1.27 to 9.43) for workers exposed to formaldehyde at 2.0–3.9 ppm and ≥4.0 ppm peak exposure, respectively (P_{trend} = .009), and 1.15 (95% CI = 0.41 to 3.23) and 2.49 (95% CI = 1.03 to 6.03) for workers exposed to formaldehyde at 0.5–0.9 ppm and ≥1.0 ppm average exposure intensity, respectively (P_{trend} = .088) (Tables 3 and 4). When we excluded peak exposures in jobs of short duration (<1 year) or peaks that occurred less often than daily, relative risks for all leukemi associated with peak exposure were not substantially changed The association of duration of exposure with leukemia wa weak, and there was no association of cumulative exposure witl leukemia (Tables 5 and 6).

Increased relative risks for all leukemia by peak and averag intensity of formaldehyde exposure were similar within catego ries of age, pay, exposure to formaldehyde-containing particu lates, and employment as a chemist or laboratory technicia (data not shown).

Table 4. Relative risks for mortality from lymphohematopoietic malignancies by average intensity of exposure to formaldehyde

Cause of death (ICD*)	Relative risk (95% confidence interval)† No. of deaths — Average intensity, ppm‖ 0	0.1–0.4	0.5–0.9	≥1.0	P_{trend}‡	P_{trend}§
Lymphohematopoietic malignancies (200–209)	0.91 (0.52 to 1.59) 17	1.00 (Referent) 81	1.63 (1.11 to 2.37) 42	1.50 (1.01 to 2.24) 38	.050	.062
Non-Hodgkin's lymphoma (200, 202)	1.02 (0.36 to 2.86) 5	1.00 (Referent) 25	1.33 (0.65 to 2.71) 11	0.98 (0.43 to 2.20) 8	.690	.607
Hodgkin's disease (201)	0.46 (0.05 to 3.93) 1	1.00 (Referent) 7	4.70 (1.61 to 13.77) 8	3.12 (0.91 to 10.74) 5	.022	.031
Multiple myeloma (203)	1.88 (0.62 to 5.65) 5	1.00 (Referent) 14	1.50 (0.60 to 3.74) 7	1.42 (0.56 to 3.58) 7	(.855)	(.801)
Leukemia (204–207)	0.56 (0.19 to 1.66) 4	1.00 (Referent) 32	1.52 (0.83 to 2.79) 16	1.68 (0.91 to 3.08) 17	.193	.242
Lymphatic leukemia (204)	0.00 (0.00 to 2.02) 0	1.00 (Referent) 9	1.56 (0.52 to 4.65) 5	1.43 (0.47 to 4.34) 5	.495	.632
Myeloid leukemia (205)	0.41 (0.08 to 1.95) 2	1.00 (Referent) 14	1.15 (0.41 to 3.23) 5	2.49 (1.03 to 6.03) 9	.086	.088
Other/unspecified leukemia (207)	1.27 (0.25 to 6.40) 2	1.00 (Referent) 9	1.69 (0.56 to 5.12) 5	0.98 (0.26 to 3.71) 3	(.697)	(.710)
No. of person-years	135 396	454 927	139 628	135 757		

*Codes of the International Classification of Diseases (ICD), 8th revision.

†Relative risks were derived from Poisson regression stratified for calendar year, age (both in 5-year intervals), sex, and race/ethnicity (black/white), and adjusted for pay category (salary/wage). Cut points for formaldehyde exposure categories were approximately the 60th and 80th percentiles of the distribution of the respective exposure measure in exposed subjects who died from cancer. These cut points ensured that there were sufficient numbers of cases in the exposed categories.

‡Two-sided likelihood ratio test (1 degree of freedom) of zero slope for continuous formaldehyde exposure among unexposed and exposed person-years; parentheses indicate negative slope estimate.

§Two-sided likelihood ratio test (1 degree of freedom) of zero slope for continuous formaldehyde exposure among exposed person-years only; parentheses indicate negative slope estimate.

‖Exposure was calculated using a 2-year lag interval.

We found evidence of an association between Hodgkin's disease (21 deaths) and exposure to formaldehyde. Compared with workers exposed to low levels of formaldehyde (0.1–1.9 ppm peak exposure or 0.1–0.4 ppm average exposure intensity), relative risks for Hodgkin's disease were 3.45 (95% CI = 0.98 to 12.16) and 3.35 (95% CI = 0.97 to 11.59) among workers

Table 5. Relative risks for mortality from lymphohematopoietic malignancies by cumulative exposure to formaldehyde

Cause of death (ICD*)	Relative risk (95% confidence intervals)† No. of deaths — Cumulative exposure, ppm-years‖ 0	0.1–1.4	1.5–5.4	≥5.5	P_{trend}‡	P_{trend}§
Lymphohematopoietic malignancies (200–209)	0.74 (0.42 to 1.30) 17	1.00 (Referent) 94	0.79 (0.52 to 1.21) 29	1.03 (0.70 to 1.52) 38	.157	.202
Non-Hodgkin's lymphoma (200, 202)	0.82 (0.29 to 2.34) 5	1.00 (Referent) 27	0.53 (0.22 to 1.31) 6	0.92 (0.45 to 1.88) 11	.968	.969
Hodgkin's disease (201)	0.29 (0.04 to 2.34) 1	1.00 (Referent) 12	1.35 (0.45 to 3.99) 5	1.17 (0.31 to 4.46) 3	.037	.045
Multiple myeloma (203)	1.49 (0.50 to 4.46) 5	1.00 (Referent) 17	0.62 (0.21 to 1.85) 4	1.03 (0.42 to 2.52) 7	(.877)	(.899)
Leukemia (204–207)	0.48 (0.16 to 1.42) 4	1.00 (Referent) 35	0.90 (0.47 to 1.73) 13	1.14 (0.63 to 2.07) 17	.183	.235
Lymphatic leukemia (204)	0.00 (0.00 to 1.67) 0	1.00 (Referent) 10	0.72 (0.20 to 2.63) 3	1.20 (0.43 to 3.33) 6	.406	.476
Myeloid leukemia (205)	0.32 (0.07 to 1.51) 2	1.00 (Referent) 17	0.57 (0.19 to 1.73) 4	1.02 (0.40 to 2.55) 7	.123	.157
Other/unspecified leukemia (207)	1.37 (0.26 to 7.20) 2	1.00 (Referent) 8	1.60 (0.51 to 5.01) 5	1.28 (0.38 to 4.36) 4	(.740)	(.783)
No. of person-years	135 396	494 579	135 240	100 493		

*Codes of the International Classification of Diseases (ICD), 8th revision.

†Relative risks were derived from Poisson regression stratified for calendar year, age (both in 5-year intervals), sex, and race/ethnicity (black/white), and adjusted for pay category (salary/wage). Cut points for formaldehyde exposure categories were approximately the 60th and 80th percentiles of the distribution of the respective exposure measure in exposed subjects who died from cancer. These cut points ensured that there were sufficient numbers of cases in the exposed categories.

‡Two-sided likelihood ratio test (1 degree of freedom) of zero slope for continuous formaldehyde exposure among unexposed and exposed person-years; parentheses indicate negative slope estimate.

§Two-sided likelihood ratio test (1 degree of freedom) of zero slope for continuous formaldehyde exposure among exposed person-years only; parentheses indicate negative slope estimate.

‖Exposure was calculated using a 2-year lag interval.

Table 6. Relative risks for mortality from lymphohematopoietic malignancies by duration of exposure to formaldehyde

Cause of death (ICD*)	Relative risk (95% confidence interval)† No. of deaths — Duration of exposure, y‖ 0	0.1–4.9	5.0–14.9	≥15.0	P_{trend}‡	P_{trend}§
Lymphohematopoietic malignancies (200–209)	0.75 (0.42 to 1.31) 17	1.00 (Referent) 90	0.74 (0.47 to 1.18) 24	1.07 (0.73 to 1.55) 47	.905	(.752)
Non-Hodgkin's lymphoma (200, 202)	0.86 (0.29 to 2.49) 5	1.00 (Referent) 25	0.56 (0.21 to 1.49) 5	0.98 (0.49 to 1.96) 14	(.613)	(.512)
Hodgkin's disease (201)	0.23 (0.03 to 1.85) 1	1.00 (Referent) 14	0.77 (0.24 to 2.45) 4	0.59 (0.12 to 2.93) 2	(.799)	(.422)
Multiple myeloma (203)	1.44 (0.48 to 4.35) 5	1.00 (Referent) 17	0.36 (0.08 to 1.57) 2	1.05 (0.45 to 2.43) 9	(.706)	.980
Leukemia (204–207)	0.55 (0.18 to 1.66) 4	1.00 (Referent) 30	1.16 (0.59 to 2.26) 13	1.39 (0.78 to 2.49) 22	.214	.465
Lymphatic leukemia (204)	0.00 (0.00 to 2.51) 0	1.00 (Referent) 7	1.87 (0.58 to 6.05) 5	1.62 (0.55 to 4.74) 7	.498	.684
Myeloid leukemia (205)	0.34 (0.07 to 1.67) 2	1.00 (Referent) 15	0.49 (0.14 to 1.73) 3	1.35 (0.56 to 3.24) 10	.423	.911
Other/unspecified leukemia (207)	1.36 (0.25 to 7.23) 2	1.00 (Referent) 8	1.49 (0.44 to 5.09) 4	1.30 (0.41 to 4.13) 5	.402	.292
No. of person-years	135 396	498 167	134 963	97 182		

*Codes of the International Classification of Diseases (ICD), 8th revision.

†Relative risks were derived from Poisson regression stratified for calendar year, age (both in 5-year intervals), sex, and race/ethnicity (black/white), and adjusted for pay category (salary/wage). Cut points for formaldehyde exposure categories were approximately the 60th and 80th percentiles of the distribution of the respective exposure measure in exposed subjects who died from cancer. These cut points ensured that there were sufficient numbers of cases in the exposed categories.

‡Two-sided likelihood ratio test (1 degree of freedom) of zero slope for continuous formaldehyde exposure among unexposed and exposed person-years; parentheses indicate negative slope estimate.

§Two-sided likelihood ratio test (1 degree of freedom) of zero slope for continuous formaldehyde exposure among exposed person-years only; parentheses indicate negative slope estimate.

‖Exposure was calculated using a 2-year lag interval.

exposed to formaldehyde at 2.0–3.9 ppm and ≥4.0 ppm peak exposure, respectively (P_{trend} = .042), and 4.70 (95% CI = 1.61 to 13.77) and 3.12 (95% CI = 0.91 to 10.74) for workers exposed at 0.5–0.9 ppm and ≥1.0 ppm average exposure intensity, respectively (P_{trend} = .031) (Tables 3 and 4). A trend was also observed for cumulative exposure (P_{trend} = .045) (Table 5). Neither non-Hodgkin's lymphoma nor multiple myeloma was associated with any of the formaldehyde exposure measures (Tables 3–6).

Because information on exposure ended in 1980, exposure may have been underestimated for some subjects who were exposed after 1980. However, the underestimate would be small because only 3.7% of all person-years were contributed by workers aged 65 years or younger and in exposed jobs in 1980. When those person-years were excluded from the analysis, the results did not change.

Potential Confounding by Exposure to Substances Other Than Formaldehyde

Forty-seven percent of the cohort members were ever exposed in the workplace to at least one of the following substances: antioxidants (22%), asbestos (14%), carbon black (11%), dyes and pigments (16%), hexamethylenetetramine (15%), melamine (28%), phenol (14%), plasticizers (20%), urea (27%), wood dust (10%), and benzene (2%). Of those ever exposed to benzene, there were six deaths from lymphohematopoietic malignancies, including one from myeloid leukemia. Only 8% of the cohort ever worked as chemists or laboratory technicians, and only 2% worked in such jobs for 5 or more years. Duration of exposure to dyes and pigments, melamine, and plasticizers was associated with all leukemia mortality (data not shown). Working as a chemist or laboratory technician was also associated with leukemia mortality (data not shown). The small numbers precluded a detailed evaluation of associations with benzene.

Relative risk estimates for myeloid leukemia, all leukemias, and all lymphohematopoietic malignancies did not change substantially, compared with the unadjusted analysis, when analyses were adjusted for duration of exposure to each of the 10 other substances and for working as a chemist or laboratory technician. We also repeated all analyses excluding the 586 subjects exposed to benzene and found no substantial differences between those results and the results of the analysis including all subjects.

Peak exposure and average exposure intensity were not evaluated in the previous analysis of this cohort *(7)*. We evaluated the earlier data for associations with these exposure measures by limiting the analysis to follow-up through 1980, and found that relative risks for leukemia (25 deaths) and the exposure categories shown in Tables 3 and 4 for peak exposure were 1.00, 1.00, 1.68, and 1.49 (P_{trend} = .423) and for average intensity were 0.89, 1.00, 1.50, and 1.35 (P_{trend} = .863). Increased relative risks for medium- and high-exposure categories show that there was some indication of an association in the earlier follow-up.

Discussion

We observed an association between mortality from leukemia, particularly for myeloid leukemia, and several indices of potential exposure to formaldehyde among industrial workers.

On the basis of our results and those previously reporting more leukemia than expected among professional workers exposed to formaldehyde *(14)*, it appears that formaldehyde may cause leukemia in humans. The association found between Hodgkin's disease and formaldehyde exposure is more difficult to interpret because it has not been observed previously.

Increased SMRs and relative risks for lymphohematopoietic malignancies have been reported in several studies of professionals exposed to formaldehyde *(14–19)* and occasionally among industrial workers *(14,20)*. In several of these studies, the excess of leukemia was mainly due to myeloid leukemia *(16–19)*, a finding that also emerged from our data.

Our findings can be compared with recent results from extended follow-ups of two other cohort studies of formaldehyde-exposed workers. Among 14 014 men employed in the British formaldehyde industry, there were fewer deaths than expected from leukemia overall (31 deaths observed versus 34.1 deaths expected) and among workers in high-exposure jobs (eight deaths observed versus 11.3 deaths expected) *(21)*. The study by Coggon et al. *(21)* was similar to ours in that it included quantitative estimates of formaldehyde exposure from production of urea and melamine formaldehyde resins, but it differed from ours in that peak exposure and average exposure intensity were not evaluated and in that our study had more than twice the number of deaths from leukemia. In a National Institute for Occupational Safety and Health cohort study of 11 039 textile workers with potential exposure to formaldehyde, researchers found an increase in leukemia mortality with longer duration of employment, i.e., SMRs (number of deaths) = 0.96 (seven), 0.72 (five), and 1.53 (12) for <3, 3–9, and ≥10 years, respectively *(22)*. The increase in SMR with duration of employment was similar to the increasing relative risks associated with duration of exposure in our study.

Experimental evidence regarding the effects of formaldehyde at sites other than the upper respiratory tract is inconsistent. Some biologic evidence suggests that carcinogenic effects of formaldehyde at non–upper respiratory tract sites would be unlikely. For example, nearly the total inhaled dose of formaldehyde is deposited in the upper respiratory tract after long-term inhalation in rats *(23)*, blood levels of formaldehyde did not change after inhalation exposure to formaldehyde in rats or humans *(24)*, and, after rats inhaled radioactively labeled formaldehyde, substantial concentrations of radioactivity were localized in bone marrow DNA, but there was no indication that inhaled formaldehyde formed adducts or cross-links with bone marrow macromolecules *(25)*.

However, other experimental evidence supports the epidemiologic findings by suggesting that formaldehyde is associated with toxicity at sites remote from the respiratory tract. For example, increased frequencies of micronuclei *(26–28)*, sister chromatid exchanges *(28–31)*, chromosomal aberrations *(28,32)*, and DNA–protein cross-links *(6,30)* have been found in peripheral lymphocytes of humans exposed to formaldehyde. Other studies *(33–37)* found some of these anomalies. Although there is a clear link between chromosomal aberrations and cancer *(38)*, the relationships between micronuclei or sister chromatid exchanges and health risks are not well documented *(39)*. In rats, long-term inhalation of formaldehyde vapor at low concentrations of 0.6 and 1.8 ppm was associated with dose-related bone marrow cytotoxicity, including chromosomal aberrations and aneuploidy *(40)*, although short-term exposure to formaldehyde at high concentrations of 15 ppm was not *(41)*. A statistically significant dose-related increase in leukemia incidence was observed in Sprague-Dawley rats administered 10–1500 ppm formaldehyde in drinking water for 2 years *(42)*, but not in Wistar rats *(43,44)*. It appears that formaldehyde-induced mutagenesis involves mainly small-scale chromosomal rearrangements rather than point mutations *(45)*. Small-scale chromosomal rearrangements are reminiscent of karyotypic anomalies found in the hematopoietic stem cells of many patients with lymphohematopoietic malignancies *(46)*. Hematopoietic stem cells are found in the bone marrow and in the peripheral blood. In peripheral blood, they could be exposed to the potentially toxic effects of formaldehyde, although the clinical significance of such exposures in leukemogenesis is unclear.

In this study, leukemia was associated with peak exposure to formaldehyde and, to a lesser degree, average exposure intensity and duration of exposure, but not with cumulative exposure. Multiple measures of exposure can complicate the interpretation of results when the measure that best characterizes delivered dose is unknown, as with formaldehyde. The initial interpretation of the results focused on whether any of the measures of formaldehyde exposure was associated with leukemia. By using four exposure measures rather than only one, we substantially reduced the risk of an overall false-negative finding. Although using four measures increased the chance of a false-positive result for a single exposure measure, we limited the possibility of a false-positive error for each measure by evaluating several aspects of a potential exposure–response relationship (i.e., increasing relative risks with categories of exposure, statistically significantly elevated relative risks, and statistically significant trends). We then interpreted the pattern of the exposure measures for which an association was or was not found. Observing generally weaker or no associations for duration of exposure than for metrics of intensity, e.g., average exposure intensity or peak exposure, was not surprising because duration as a measure of exposure assumes a constant exposure rate for all jobs and over time, which does not hold in this study. Therefore, the use of duration of exposure to evaluate associations results in substantial exposure misclassification. However, the absence of an association between cumulative exposure and leukemia given the associations with the other three exposure measures was unexpected.

Risk estimates could be confounded by other occupational exposures. However, our findings of the association between formaldehyde exposure and leukemia are not explained by exposure to 11 other agents used in these industrial plants or by working as a chemist or laboratory technician. We were concerned about benzene, a known risk factor for leukemia, and found no difference in the results when all workers exposed to benzene were excluded from the analyses. Although tobacco exposure has been weakly linked with leukemia *(47)*, it is unlikely to explain our findings because there was no consistent increase in tobacco-related diseases, including lung cancer, among the cohort. Information on smoking from medical records for a sample of 63 workers with cancer and 316 age-matched control subjects from two plants revealed no major differences in smoking prevalence by level of exposure to formaldehyde *(8)*. Analyses were not adjusted for plant for two reasons. First, we directly addressed confounding by factors potentially associated with plant by adjusting for 11 potentially confounding substances. Second, adjusting for plant may potentially result in

overadjustment. However, to address the potential effect of unmeasured confounders associated with plant, we performed analyses adjusted for plant and separately by plant type (resins, four plants; plywood, one plant; film, two plants; formaldehyde and resins, three plants). Although some of these analyses were based on small numbers and, as a consequence, estimates had large variances, associations for leukemia and Hodgkin's disease found in the adjusted analyses were similar to those in the analyses that did not adjust for plant.

One potential limitation of our study was exposure misclassification. The detailed approach to developing quantitative estimates of time-weighted average exposure intensity by using monitoring data provided by the companies, monitoring in each plant by study investigators *(13)*, having study industrial hygienists visit the plants, and discussing exposure with plant managers and long-time workers *(9)* should have minimized misclassification of average and cumulative exposure and of duration of exposure. The assessment of peak exposure could have been more susceptible to misclassification because peak levels were estimated from time-weighted average exposure and job tasks. However, any exposure misclassification should be nondifferential with respect to disease status in a cohort study, in which exposure is assessed before disease outcome, and this nondifferential exposure misclassification would attenuate exposure–response patterns. Moreover, associations with peak exposure changed little when peak exposures in jobs of short duration (<1 year) and when peak exposures that occurred less often than daily were excluded from the analyses. Therefore, exposure misclassification is unlikely to be responsible for the positive findings in our study.

A second potential limitation was the lack of information on exposures during the recent follow-up (1980–1994), which could cause an underestimation of exposure for individuals working after 1980. However, the impact would be minimal because only a small proportion of individuals was likely exposed after 1980 (3.7% of all person-years) and, for those workers, levels of exposure were probably considerably lower after 1980 than in earlier years. Although the accuracy of death certificates for lymphohematopoietic malignancies is generally high, classification of subtypes of leukemia and lymphoma from death certificates is less accurate than classification from hospital records *(48)*. However, in this study, any disease misclassification should be nondifferential with respect to formaldehyde exposure. In our follow-up, individuals not identified as deceased by the National Death Index Plus were assumed to be alive. Although a violation of this assumption could result in some underascertainment of deaths, underascertainment is unlikely to be related to formaldehyde exposure and, therefore, should not have biased the results.

Our study has several major strengths, including its large size (up to 60 years of follow-up and 178 deaths from lymphohematopoietic malignancies) and the extensive assessment of formaldehyde exposure by using several measures (peak, average, cumulative, and duration of exposure). Because these measures were only moderately correlated *(10)*, they classify workers differently and provide relatively independent assessments of exposure–response. Duration of exposure to formaldehyde was poorly correlated with peak exposure or average intensity [Pearson correlation coefficients were 0.3 and 0.0, respectively *(10)*], which may explain its lack of association with leukemia. In addition, we did not rely on external comparisons (i.e., SMRs), which are subject to a healthy worker bias *(49)*, but instead focused on internal analyses that compared similar individuals.

In summary, the increased risk for leukemia mortality, particularly myeloid leukemia, from peak and average exposure to formaldehyde could not be explained by obvious biases or confounding. The exposure–response gradient observed and the consistency with other epidemiologic studies of workers in occupations with formaldehyde exposure and some experimental studies suggest a causal association between formaldehyde exposure and leukemia. However, lack of an association in a recent follow-up of a similar but smaller industrial cohort in Great Britain *(21)* introduces uncertainty regarding the relationship.

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