Mortality From Lymphohematopoietic Malignancies Among Workers in Formaldehyde Industries: The National Cancer Institute Cohort

Laura E. Beane Freeman, Aaron Blair, Jay H. Lubin, Patricia A. Stewart, Richard B. Hayes, Robert N. Hoover, Michael Hauptmann

Background Formaldehyde exposure is associated with leukemia in some epidemiological studies. In the National Cancer Institute's formaldehyde cohort, previously followed through December 31, 1979, and updated through December 31, 1994, formaldehyde exposure was associated with an increased risk for leukemia, particularly myeloid leukemia, that increased with peak and average intensity of exposure.

Methods We extended follow-up through December 31, 2004 (median follow-up = 42 years), for 25 619 workers employed at one of 10 formaldehyde-using or formaldehyde-producing plants before 1966. We used Poisson regression to calculate relative risk (RR) estimates and 95% confidence intervals (CIs) to examine associations between quantitative formaldehyde exposure estimates (peak exposure, average intensity and cumulative exposure) and death from lymphohematopoietic malignancies. All statistical tests were two-sided and considered to be significant at $P = .05$.

Results When follow-up ended in 2004, there were statistically significant increased risks for the highest vs lowest peak formaldehyde exposure category (≥4 parts per million [ppm] vs >0 to <2.0 ppm) and all lymphohematopoietic malignancies (RR = 1.37; 95% CI = 1.03 to 1.81, P trend = .02) and Hodgkin lymphoma (RR = 3.96; 95% CI = 1.31 to 12.02, P trend = .01). Statistically nonsignificant associations were observed for multiple myeloma (RR = 2.04; 95% CI = 1.01 to 4.12, P trend > .50), all leukemia (RR = 1.42; 95% CI = 0.92 to 2.18, P trend = .12), and myeloid leukemia (RR = 1.78; 95% CI = 0.87 to 3.64, P trend = .13). There was little evidence of association for any lymphohematopoietic malignancy with average intensity or cumulative exposure at the end of follow-up in 2004. However, disease associations varied over time. For peak exposure, the highest formaldehyde-related risks for myeloid leukemia occurred before 1980, but trend tests attained statistical significance in 1990 only. After the mid-1990s, the formaldehyde-related risk of myeloid leukemia declined.

Conclusions Evaluation of risks over time suggests a possible link between formaldehyde exposure and lymphohematopoietic malignancies, particularly myeloid leukemia but also perhaps Hodgkin lymphoma and multiple myeloma. Observed patterns could be due to chance but are also consistent with a causal association within the relatively short induction–incubation periods characteristic of leukemogenesis. Further epidemiological study and exploration of potential molecular mechanisms are warranted.

J Natl Cancer Inst 2009;101:751–761

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

Formaldehyde is widely used for various industrial purposes and as a preservative and disinfectant. In 2000, annual US formaldehyde production exceeded 4.6 million tons (1). The Occupational Safety and Health Administration (OSHA) estimated that in 1995 approximately 2.1 million people in the United States were exposed to formaldehyde in the workplace (2). A substantially larger number of people may be exposed to lower environmental levels.

The International Agency for Research on Cancer (IARC) recently classified formaldehyde as a human carcinogen, primarily because of its association with nasopharyngeal cancer in humans and nasal cancer in rodents. The evidence for a causal association between leukemia and occupational exposure to formaldehyde was deemed inconclusive because of inconsistencies in the epidemiological literature and uncertainty about mechanisms of leukemogenicity

Affiliations of authors: Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD.

Correspondence to: Laura E. Beane Freeman, PhD, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 6120 Executive Blvd, EPS/8112 Rockville, MD 20892 (e-mail: freemala@mail.nih.gov).

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djp096

© The Author 2009. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.

CONTEXT AND CAVEATS

Prior knowledge

Previous analysis of data from a cohort of workers in formaldehyde industries and data from other epidemiologic studies suggested that exposure to this carcinogen was associated with increased risk of leukemia.

Study design

Prospective cohort study of workers who had been employed in formaldehyde industries. Exposure was estimated based on work histories, and deaths and causes of deaths were obtained from the National Death Index. Poisson regression was used to calculate risks of death from lymphohematopoietic malignancies associated with formaldehyde exposure.

Contribution

The long-term follow-up of industrial workers in this study suggested a possible association between formaldehyde exposure and mortality due to lymphohematopoetic malignancies, particularly myeloid leukemia.

Implications

Further epidemiological studies to evaluate risks of leukemia and lymphatic tumors in formaldehyde-exposed populations are warranted.

Limitations

This study relied on death certificate data, which may lack specificity with respect to sub-types of disease.

From the Editors

(3). Since the 1980s, the National Cancer Institute (NCI) has studied a cohort of workers in formaldehyde-producing and formaldehyde-using plants to evaluate cancer risks (4). In the most recent report, which made use of follow-up data through 1994, it was found that relative risks (RRs) for lymphohematopoietic malignancies, including leukemia, and in particular myeloid leukemia, increased with increasing peak- and average-intensity formaldehyde exposure (5). In this analysis, we extended the mortality follow-up by 10 years to further examine associations between formaldehyde exposure and mortality from lymphohematopoietic malignancies and the evolution of these associations over time.

Methods

Cohort Design and Follow-up

The cohort consists of 25 619 workers employed in one of 10 industrial plants in the United States before January 1, 1966. The 10 plants were manufacturers of formaldehyde, formaldehyde resins, or molding compounds or were major users of formaldehyde resins or molding compounds, including molded plastic products, decorative laminates, photographic film, and plywood. The original study included deaths through 1979 (4); an extension of this study added deaths from the beginning of 1980 through December 31, 1994 (5,6).

Before 1980, vital status of cohort members was determined using data from the Social Security Administration, the Health Care Financing Administration, the Veterans Administration, credit bureaus, motor vehicle departments, and telephone directories. For deaths reported before 1980, death certificates were obtained to determine the underlying cause of death. After 1980, the cohort was traced using the National Death Index Plus (NDI Plus) (http://www.cdc.gov/nchs/r&d/ndi/ndi.htm) through December 31, 2004. In this update, we found 1006 deaths that occurred between 1980 and 1994 that had not been included in previous analyses (5,6), and we explored why these deaths were not identified in the previous linkage. There was no apparent change in NDI procedures for assigning matches, and the matching scores provided by NDI for those 1006 not included in the previous analyses were not different from those that were included. For this reason, we believe that the additional deaths are not due to a systematic liberalization of matching criteria. We were unable to access the full file provided by NDI after the initial 1994 linkage to further explore potential reasons for the discrepancy. Therefore, we do not have an explanation for why these 1006 deaths were not included in the previous analyses. We have assumed that these deaths represent the actual experience of the cohort, and we have included them in all analyses for this update. We also identified four individuals previously considered deceased (one who died from other or unspecified leukemia, two with chronic ischemic heart disease, one who died as a result of assault by firearms or explosives) who we did not consider to be deceased in current analyses. For deaths occurring between 1980 and 2004, we used the underlying cause of death reported by NDI Plus, as opposed to relying upon manual coding as was done in previous analyses (5,6). Relying on NDI Plus cause of death resulted in changing the cause of death for six individuals from a lymphohematopoietic malignancy to some other cause (one multiple myeloma to melanoma, one myeloid leukemia to neoplasm of unspecified nature of other and unspecified organs, one non-Hodgkin lymphoma to pneumococcal pneumonia, and three myelofibrosis to other diseases of blood forming organs, neoplasm of unspecified nature, or septicemia). In two instances, the original cause of death (lung cancer and pneumococcal pneumonia) was changed to a lymphohematopoietic malignancy (multiple myeloma in both cases). These changes did not substantively affect previously reported results. After the addition and recoding of causes of death, the relative risks with follow-up through 1994 for the highest category of peak exposure compared with the lowest were increased for all lymphohematopoietic malignancies (RR = 1.48; 95% CI = 1.04 to 2.12, P trend = .03), Hodgkin lymphoma (RR = 3.30; 95% CI = 0.98 to 11.10, P trend = .04), multiple myeloma (RR = 2.03; 95% CI = 0.89 to 4.64, P trend = .14), all leukemia (RR = 1.60; 95% CI = 0.90 to 2.82, P trend = .09), and myeloid leukemia (RR = 2.79; 95% CI = 1.08 to 7.21, P trend = .02). For average intensity, the relative risk in the highest category was 1.25 (95% CI = 0.85 to 1.83, P trend = .40), 3.06 (95% CI = 0.90 to 10.35, P trend = .03), 1.39 (95% CI = 0.59 to 3.29, P trend > .50), 1.34 (95% CI = 0.74 to 2.41, P trend > .50), and 2.19 (95% CI = 0.92 to 5.25, P trend = .11), for all lymphohematopoietic malignancies, Hodgkin lymphoma, multiple myeloma, all leukemia, and myeloid leukemia, respectively. The full revised results for follow-up through 1994 are available in Supplementary Tables 1–4 (available online).

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

We did not contact study participants, and the National Institutes of Health Office of Human Subjects Research determined that the study was exempt from an Institutional Review Board review. When it was necessary to obtain death certificates, we obtained approval from individual state institutional review boards.

Exposure Assessment

A comprehensive description of exposure assessment was given in previous reports (4,7,8). Exposure to formaldehyde was estimated for each job from individual work histories abstracted in 1980. Calendar time- and plant-specific estimates were made on the basis of expert assessment of job and department titles and tasks associated with the jobs by using current and past measurement data. For each job, continuous 8-hour, time-weighted average formaldehyde intensity (TWA8) (expressed in parts per million [ppm]) was estimated. Because excess leukemia mortality had been observed in several surveys of anatomists, pathologists, and embalmers, possibly due to their intermittent exposure to relatively high levels of formaldehyde, categorical levels of peak exposure (none, >0 to <0.5 ppm, 0.5 to <2.0 ppm, 2.0 to <4.0 ppm, or ≥4.0 ppm) and peak frequency (monthly, weekly, daily, or hourly) were estimated. Peak exposures were defined as short-term exposures (generally less than 15 minutes) that exceeded the TWA8 category. The TWA8 categories were developed before the estimation process to reflect the approximate levels of sensory experiences of detectable odor and eye irritation and tearing. Peak exposures could be related to either routine or nonroutine high-exposure tasks or could result from nonroutine unusual events, such as spills. Peak frequency was estimated on the basis of knowledge of the job and the likelihood that a high-exposure task or event would occur. Because there was no direct information on frequency of peaks, a higher degree of uncertainty is associated with the frequency than the level of peak exposure. The presence of formaldehyde-containing particulates and exposure to other widely used chemicals in the plants were identified (eg, antioxidants, asbestos, benzene, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, and wood dust).

Statistical Analysis

Deaths from lymphohematopoietic malignancies and selected subtypes were grouped on the basis of the *International Classification of Diseases, Eighth Revision* (ICD-8) classification. We also classified lymphohematopoietic malignancies as arising from lymphoid (Hodgkin lymphoma, non-Hodgkin lymphoma, multiple myeloma, or lymphatic leukemia, with the ICD-8 codes 200, 201, 202, 203, or 204) or nonlymphoid cell lineages (myeloid leukemia, monocytic leukemia, polycythemia vera, or myelofibrosis, with the ICD-8 codes 205, 206, 208, or 209).

Subjects contributed person–time at risk from year of first employment at the plant (1930–1966) or cohort identification (1934–1958), whichever was later, through loss to follow-up (n = 676), the date of death, or December 31, 2004, whichever was earlier.

We developed time-dependent formaldehyde exposure indices. Study participants contributed time to the nonexposed category until they became exposed, at which time they contributed person–time to the appropriate exposure category on the basis of the level of exposure for all previous jobs. Duration of exposure (years) was the total time in exposed jobs. Cumulative exposure (ppm-years) was the product of the duration of formaldehyde exposure in years and the TWA8 in parts per million in each job summed across all jobs. Average intensity (ppm) was the total cumulative exposure divided by duration (years) of exposure. For the calculation of maximum peak exposure, jobs not identified as having peak exposure levels that exceeded the TWA8 category were assigned the TWA8 intensity category as peak level because it was considered to reflect the maximum level of intensity in those jobs. For analysis, we used four peak exposure categories (none, >0 to <2.0 ppm, 2.0 to <4.0 ppm, or ≥4.0 ppm). Despite uncertainties associated with estimates of peak frequency, relative risk by frequency of peaks ≥4.0 ppm was also evaluated. The number of peaks exceeding ≥4.0 ppm and corresponding to hourly, daily, weekly, or monthly peak frequency was set to 2000, 250, 50, or 8.2 per year employed in a job, respectively, and summed across all jobs with peaks ≥4.0 ppm. To ensure an adequate number of cancer cases in the exposed categories, analytic categories were based on the approximate 60th and 80th percentiles among exposed subjects who died from cancer for average intensity and cumulative exposure (0.1 to <0.5, 0.5 to <1.0, ≥1.0 ppm and ≥0 to 1.5, 1.5 to <5.5, ≥5.5 ppm-year, respectively).

Standardized mortality ratios (SMRs) were calculated using sex-, race-, age-, and calendar-year–specific US mortality rates (9). Relative risks were estimated with Poisson regression analysis; stratified for calendar year (5-year categories), age (5-year categories), sex, and race (white or other); and adjusted for pay category (salary, ever wage, or unknown). When calculating the relative risks, the lowest nonzero category of exposure was considered to be the most appropriate referent group. We calculated trend tests on the basis of all person-years and on exposed person–years only. Unless otherwise stated, reported trend test *P* values were based on exposed person–time. For average intensity and cumulative exposure, trend tests were based on the likelihood ratio for the regression coefficient of the continuous exposure variable. For peak exposure, category ranks were used for the trend tests. Heterogeneity of exposure-specific relative risk estimates by race, gender, and pay category was examined by comparing stratum-specific risk estimates using likelihood ratio tests.

We calculated cumulative relative risks by moving the end of follow-up forward in yearly increments starting in 1965 to examine the change in associations with the accrual of person–time and events. For peak and average intensity of exposure, we plotted the relative risks for the medium- and high-exposure categories and calculated *P* values for the trend in the exposed by year of end of follow-up. The final points on the graphs correspond to relative risk estimates and trend *P* values for follow-up ending in 2004 (presented in Tables 2 and 3). We also evaluated the relative risk for myeloid leukemia by nonoverlapping time periods corresponding to the calendar time of the first report (before 1981), the 2003 report (1981–1994), and the added follow-up in this report (1995–2004). We evaluated risks by time since the start of the first formaldehyde-exposed job, with 15 or fewer years before as the referent category, and time since first peak exposure of greater than 4.0 ppm, with 25 or fewer years as the referent category.

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

We evaluated confounding by controlling for duration (0, ≥0 to <5, ≥5 years) of working as a chemist or laboratory technician because of potential exposure to the known leukemogen benzene, exposure to formaldehyde-containing particulates, and exposure to 11 substances (antioxidants, asbestos, benzene, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, and wood dust) that may be either associated with formaldehyde exposure or with lymphohematopoietic malignancies. We also performed analyses excluding persons potentially exposed to benzene, evaluated the effect of salaried and wage workers separately, and performed plant-adjusted analyses.

We used a 2-year lag interval for all exposure indices for consistency with previous analyses (5). We evaluated lag intervals from 2 through 25 years by person–time for which exposure was available, that is, by censoring subjects in 1980 plus the lag time for each evaluated lag period, and found that longer lags of around 18 years best fit the data, although they did not change the risk estimates. Because there was not strong support for assuming that either a longer or a shorter lag was most appropriate, we report results with a 2-year lag.

For each formaldehyde exposure metric except peak exposure, which was inherently categorical, we evaluated departure from linearity of the relationship between the log relative risk and formaldehyde exposure by assessing the statistical significance of a quadratic curvature term in a model with the continuous exposure metric fitted to the exposed only. No evidence of nonlinearity was observed.

Estimates of formaldehyde exposures after 1980 were not developed, as this was the last year the work records were abstracted; in the primary analyses, we assumed zero exposure occurred after this date. We carried out two sensitivity analyses to evaluate this assumption. First, we assigned a maximum likely exposure by assuming that subjects who were in exposed jobs in 1980 remained exposed at this level until age 65 years, death, or the end of the study, whichever came first. This assignment affected 2809 individuals, with 35 422 person-years of follow-up (3.5% of total person-years). In a second approach, we censored the follow-up 2 years after the end of the last job for all individuals who were still exposed in 1979 and alive 2 years later (n = 2810), which reduced total person-years by 53 290 (5.3%).

All analyses were performed with EPICURE software (10), and all statistical tests were two-sided. The threshold for statistical significance was .05.

Results

Description of the Cohort

The 25 619 cohort members accrued 998 106 person-years of follow-up, and the median length of follow-up was 42 years. Overall, 92.7% of those in the cohort were white, 87.8% were male, and 78.5% were hourly workers. There were 13 951 deaths that occurred from 1943 through December 31, 2004. The median ages at entry into and exit from the study were 26 and 69 years, respectively.

There were 4359 workers who were classified as never exposed to formaldehyde. The median estimated formaldehyde TWA8 for exposed individuals was 0.3 ppm (range = 0.01–4.3 ppm), and the median cumulative exposure was 0.6 ppm-years (range = 0.0–107.4 ppm-years). There were 3927 workers with average intensity levels ≥1.0 ppm and 6255 who experienced peak formaldehyde exposures ≥4.0 ppm. Of these, 25% experienced such peaks less than 25 times and 25% experienced them more than 700 times.

Formaldehyde Exposure and Mortality

For those exposed to formaldehyde, the risk of death from all causes was similar to that in the US population (SMR = 1.02; 95% CI = 0.99 to 1.03); among those unexposed, the risk was lower (SMR = 0.90; 95% CI = 0.85 to 0.94). Standardized mortality ratios for all cancers and all solid cancers were statistically significantly elevated among the exposed (1.07; 95% CI = 1.03 to 1.11 and 1.09; 95% CI = 1.05 to 1.13, respectively), but slight deficits were observed among the unexposed (SMRs = 0.93; 95% CI = 0.84 to 1.03 and 0.94; 95% CI = 0.84 to 1.05, respectively). The 319 deaths from lymphohematopoietic malignancies resulted in similar standardized mortality ratios in exposed and unexposed (SMR = 0.94; 95% CI = 0.84 to 1.06 and SMR = 0.86; 95% CI = 0.61 to 1.21, respectively) among exposed workers and 0.86 among the unexposed (Table 1). Relative risks for death from all causes decreased with increasing peak, average intensity, and cumulative exposure levels (all three *P* values from tests of trend were less than .001, data not shown). Risks for all cancers combined decreased with increasing peak (*P* trend = .01); trends for cumulative exposure (*P* trend = .07) and average intensity of exposure (*P* trend = .22) did not attain statistical significance.

There was a statistically significant positive association between the risk of lymphohematopoietic malignancies and peak formaldehyde exposure (*P* trend = .02) (RR = 1.37; 95% CI = 1.03 to 1.81) among those with peak exposures ≥4.0 ppm compared with those with peaks ≥0 to <2.0 ppm (Table 2). For leukemia, the risk was elevated in the highest peak category (RR = 1.42; 95% CI = 0.92 to 2.18), and the *P* trend was lower when unexposed subjects were included (*P* trend = .02) than when they were not included (*P* trend = .12, Table 2). No statistically significant associations were observed with average intensity (Table 3) or cumulative exposure to formaldehyde (Table 4). For the highest peak exposure, there was a non-statistically significant elevated relative risk for myeloid leukemia (RR = 1.78; 95% CI = 0.87 to 3.64, *P* trend = .13). When including all person-years (both unexposed and exposed), the *P* trend was .07. For the highest average intensity, there was a statistically nonsignificant increase for myeloid leukemia (RR = 1.61; 95% CI = 0.76 to 3.39; *P* trend = .43). There was no evidence of an association of any lymphohematopoietic malignancies with cumulative exposure (Table 4).

Risks for Hodgkin lymphoma increased with greater peak (*P* trend = 0.01, Table 2) and average intensity of exposure (*P* trend = .05, Table 3) with two- to fourfold relative risks in higher exposure categories. Associations were weaker for cumulative exposure (*P* trend = .08, Table 4). The relative risk for multiple myeloma was elevated among workers with the highest peak exposure (RR = 2.04; 95% CI = 1.01 to 4.12, *P* trend = .08, Table 2). Unexposed subjects were at increased risk for death from multiple myeloma compared with those with the lowest nonzero levels of exposure for both peak and average intensity of exposure (Tables 2 and 3).

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

Table 1. Mortality from lymphohematopoietic malignancies among a cohort of US workers nonexposed and exposed to formaldehyde, mortality follow-up through 2004*

	Nonexposed		Exposed	
Cause of death (ICD-8 codes)	**No. observed**	**SMR (95% CI)**	**No. observed**	**SMR (95% CI)**
Lymphohematopoietic malignancies (200–209)	33	0.86 (0.61 to 1.21)	286	0.94 (0.84 to 1.06)
NHL (200, 202)	12	0.86 (0.49 to 1.52)	94	0.85 (0.70 to 1.05)
Hodgkin disease (201)	2	0.70 (0.17 to 2.80)	25	1.42 (0.96 to 2.10)
Multiple myeloma (203)	11	1.78 (0.99 to 3.22)	48	0.94 (0.71 to 1.25)
Leukemia (204–207)	7	0.48 (0.23 to 1.01)	116	1.02 (0.85 to 1.22)
Lymphatic leukemia (204)	1	0.26 (0.04 to 1.82)	36	1.15 (0.83 to 1.59)
Myeloid leukemia (205)	4	0.65 (0.25 to 1.74)	44	0.90 (0.67 to 1.21)

* Uses a 2-year lag for exposure. SMR = standard mortality ratios; ICD-8 = *International Classification of Diseases, Eighth Revision;* CI = confidence interval; NHL = non-Hodgkin lymphoma.

There was no evidence that risks increased with cumulative number of peaks ≥4.0 ppm or for duration of exposure for any cause of death evaluated (data not shown).

Effect of Factors Other Than Formaldehyde Exposure

Controlling for duration of exposure to 11 potentially confounding substances or working as a chemist or laboratory technician did not meaningfully change results (data not shown). Excluding individuals with possible benzene exposure (n = 586) did not change the relative risk for myeloid or lymphatic leukemia in the highest peak exposure category (RR = 1.77; 95% CI = 0.85 to 3.69 and RR = 1.16; 95% CI = 0.54 to 2.48, respectively) or any other cancer (data not shown). We found no evidence of heterogeneity of relative risks by race (white or other), sex, or pay category (salaried or hourly). Adjusting for plant did not substantively change results.

Effect of Unknown Post-1980 Exposures

We evaluated sensitivity of results to unknown post-1980 formaldehyde exposure. Risk patterns were similar when we assigned exposures at 1980 levels until age 65 or death. When we censored workers who were exposed in 1980, the association with myeloid leukemia was stronger for peak and average intensity of exposure: relative risks for peak exposure were 1.93 (95% CI = 0.76 to 4.90) and 2.64 (95% CI = 1.12 to 6.20) for 2.0 to <4.0 ppm and ≥4.0 ppm, respectively (*P* trend = .03), compared with 1.30 (95% CI = 0.58 to 2.92) and 1.78 (95% CI = 0.87 to 3.74) in the primary analysis (Table 2). For average intensity, the relative risks were 1.46 (95% CI = 0.62 to 3.42) and 1.75 (95% CI = 0.77 to 3.97) for 0.5–<1.0 ppm and ≥1.0 ppm, respectively (*P* trend = .37), compared with 1.21 (95% CI = 0.56 to 2.62) and 1.61 (95% CI = 0.76 to 3.39) in primary analyses (Table 3). The relative risk for myeloid leukemia for the highest category of cumulative exposure was 0.90 (95% CI = 0.35

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

Table 2. Association between peak formaldehyde exposure and death from lymphohematopoietic malignancies, mortality follow-up through 2004*

	Peak exposure (ppm)									
	0		>0 to <2.0		2.0 to <4.0		≥4.0			
Cause of death (ICD-8 codes)	**No. of deaths**	**RR (95% CI)**	**No. of deaths**	**RR (referent)**	**No. of deaths**	**RR (95% CI)**	**No. of deaths**	**RR (95% CI)**	***P* trend†**	***P* trend‡**
Lymphohematopoietic malignancies (200–209)	33	1.07 (0.70 to 1.62)	103	1.0	75	1.17 (0.86 to 1.59)	108	1.37 (1.03 to 1.81)	.02	.04
NHL (200, 202)	12	1.06 (0.53 to 2.14)	39	1.0	27	1.08 (0.65 to 1.78)	28	0.91 (0.55 to 1.49)	>.50	>.50
Hodgkin lymphoma (201)	2	0.67 (0.12 to 3.60)	6	1.0	8	3.30 (1.04 to 10.50)	11	3.96 (1.31 to 12.02)	.01	.004
Multiple myeloma (203)	11	2.74 (1.18 to 6.37)	14	1.0	13	1.65 (0.76 to 3.61)	21	2.04 (1.01 to 4.12)	.08	>.50
Leukemia (204–207)	7	0.59 (0.25 to 1.36)	41	1.0	27	0.98 (0.60 to 1.62)	48	1.42 (0.92 to 2.18)	.12	.02
Lymphatic leukemia (204)	1	0.27 (0.03 to 2.13)	14	1.0	8	0.81 (0.33 to 1.96)	14	1.15 (0.54 to 2.47)	>.50	.30
Myeloid leukemia (205)	4	0.82 (0.25 to 2.67)	14	1.0	11	1.30 (0.58 to 2.92)	19	1.78 (0.87 to 3.64)	.13	.07
Other and unspecified leukemia (207)	2	0.61 (0.13 to 2.85)	13	1.0	8	0.86 (0.35 to 2.12)	13	1.15 (0.53 to 2.53)	>.50	.50
Lymphohematopoietic malignancy of lymphoid origin (200–204)	26	1.17 (0.72 to 1.89)	73	1.0	56	1.27 (0.89 to 1.82)	74	1.35 (0.97 to 1.89)	.06	.10
Lymphohematopoietic malignancy of nonlymphoid origin (205, 206, 208, 209)	5	1.01 (0.34 to 2.98)	15	1.0	11	1.19 (0.54 to 2.62)	21	1.80 (0.91 to 3.57)	.09	.09

* All calculations used a 2-year lag. ppm = parts per million; RR = relative risk; ICD-8 = *International Classification of Diseases, Eighth Revision;* CI = confidence interval; NHL = non-Hodgkin lymphoma.

† Two-sided likelihood ratio test (1 *df*) of zero slope for continuous formaldehyde exposure among exposed person-years only.

‡ Two-sided likelihood ratio test (1 *df*) of zero slope for continuous formaldehyde exposure among unexposed and exposed person-years.

Table 3. Association between the average intensity of exposure to formaldehyde and death from lymphohematopoietic malignancies, mortality follow-up through 2004*

	Average formaldehyde intensity (ppm)									
	0		>0–<0.5		0.5–<1.0		≥1.0			
Cause of death (ICD-8 codes)	No. of deaths	RR (95% CI)	No. of deaths	RR (referent)	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)	*P* trend†	*P* trend‡
Lymphohematopoietic malignancies (200–209)	33	0.99 (0.66 to 1.48)	164	1.0	67	1.29 (0.97 to 1.73)	55	1.07 (0.78 to 1.47)	>.50	>.50
NHL (200, 202)	12	1.08 (0.55 to 2.12)	59	1.0	22	1.20 (0.73 to 1.96)	13	0.71 (0.39 to 1.32)	>.50	.40
Hodgkin lymphoma (201)	2	0.53 (0.11 to 2.66)	10	1.0	9	3.62 (1.41 to 9.31)	6	2.48 (0.84 to 7.32)	.05	.03
Multiple myeloma (203)	11	2.18 (1.01 to 4.70)	25	1.0	11	1.40 (0.68 to 2.86)	12	1.49 (0.73 to 3.04)	>.50	>.50
Leukemia (204–207)	7	0.54 (0.24 to 1.22)	67	1.0	25	1.13 (0.71 to 1.79)	24	1.10 (0.68 to 1.78)	>.50	.50
Lymphatic leukemia (204)	1	0.26 (0.03 to 2.01)	22	1.0	7	0.92 (0.39 to 2.16)	7	0.88 (0.37 to 2.11)	>.50	>.50
Myeloid leukemia (205)	4	0.70 (0.23 to 2.16)	24	1.0	9	1.21 (0.56 to 2.62)	11	1.61 (0.76 to 3.39)	.43	.40
Other and unspecified eukemia (207)	2	0.58 (0.13 to 2.62)	21	1.0	7	0.98 (0.42 to 2.33)	6	0.84 (0.33 to 2.12)	>.50	>.50
Lymphohematopoietic malignancy of lymphoid origin (200–204)	26	1.08 (0.68 to 1.71)	116	1.0	49	1.36 (0.97 to 1.90)	38	1.05 (0.72 to 1.53)	>.5	>.50
Lymphohematopoietic malignancy of nonlymphoid origin (205, 206, 208, 209)	5	0.89 (0.32 to 2.50)	25	1.0	11	1.40 (0.68 to 2.86)	11	1.51 (0.72 to 3.16)	>.5	>.50

* All calculations used a 2-year lag. ppm = parts per million; RR = relative risk; CI = confidence interval; ICD-8 = *International Classification of Diseases, Eighth Revision;* NHL = non-Hodgkin lymphoma.

† Two-sided likelihood ratio test (1 *df*) of zero slope for continuous formaldehyde exposure among exposed person-years only.

‡ Two-sided likelihood ratio test (1 *df*) of zero slope for continuous formaldehyde exposure among unexposed and exposed person-years.

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

to 2.28, *P* trend > .50) compared with 1.02 (95% CI = 0.48 to 2.16) in the primary analysis (Table 4). Patterns for other diseases were largely unchanged.

Extending End of Follow-up by Yearly Increments and Time Period Analyses

Similar to our previous report, excesses of myeloid leukemia were found in the highest peak exposure category up to 1994 (RR = 2.79; 95% CI = 1.08 to 7.21, *P* trend = 0.02). Relative risks for the two periods of follow-up until this time were 3.92 (*P* trend = .12) before 1981 and 2.70 (*P* trend = .21) for 1981–1994 for the highest peak exposure category. There was no excess in the most recent follow-up time period of 1995–2004 (RR = 0.71; *P* trend > .50). In the highest peak exposure category, the cumulative risks, calculated by extending the calendar-year of follow-up by 1 year, were elevated over the complete follow-up for myeloid leukemia (Figure 1, relative risk estimates), with statistically significant trend *P* values starting in 1990 and continuing up to 2000 (Figure 1, trend *P* value plot). Among those exposed to peaks ≥4.0 ppm, the risk of myeloid leukemia appeared highest <25 years since first peak exposure ≥4.0 ppm (data not shown). The risk was also highest in the period from 15 to 25 years since the start of the first formaldehyde-exposed job (RR = 2.44; 95% CI = 0.45 to 13.25) compared with the period <15 years since first exposure.

Cumulative risks among those in high- and medium-peak exposure categories were elevated over most of the study follow-up time for Hodgkin lymphoma and lymphohematopoietic malignancies (Figure 1). Risks for average intensity of exposure showed similar patterns, although risks were generally attenuated compared with those associated with peak exposure (Figure 2). Relative risks for all lymphohematopoietic malignancies (RR = 1.30; 95% CI = 0.68 to 2.49), leukemia (RR = 2.13; 95% CI = 0.64 to 7.15), and Hodgkin lymphoma (RR = 1.54; 95% CI = 0.42 to 5.62) were similar to myeloid leukemia in that risks were highest 15–25 years since first formaldehyde exposure.

Discussion

We found a statistically significant association between death from lymphohematopoietic malignancies and peak exposure to formaldehyde in this large cohort of workers in formaldehyde industries followed through 2004 but no association with average intensity or cumulative exposure. For peak exposure, the cumulative risk estimates, calculated by extending follow-up by yearly increments for the highest exposure category, remained statistically significant throughout but decreased when extending the follow-up beyond 1980. Relative risks with average intensity were at or near their maxima when follow-up ended in the 1980s and declined with accrual of additional person-years and events. Other studies that have examined associations with all lymphohematopoietic malignancies have reported mostly small excesses of these cancers that were based on small numbers of subjects (11–18). A cohort study of 11 039 garment workers was recently updated (19) and found no excess of all lymphohematopoietic malignancies.

The overall associations of formaldehyde exposure with leukemia and myeloid leukemia in the NCI cohort have diminished with an additional 10 years of follow-up since our previous analysis (5). For peak exposure and myeloid leukemia, the cumulative risk estimates were highest before 1980 but only achieved statistical significance in the early 1990s, after which they slowly declined. This pattern

Table 4. Association between cumulative exposure to formaldehyde and death from lymphohematopoietic malignancies, mortality follow-up through 2004*

	Cumulative exposure (ppm-year)									
	0		>0 to <1.5		1.5 to <5.5		≥5.5			
Cause of death (ICD-8 codes)	No. of deaths	RR (95% CI)	No. of deaths	RR (referent)	No. of deaths	RR (95% CI)	No. of deaths	RR (95% CI)	*P* trend†	*P* trend‡
Lymphohematopoietic malignancies (200-209)	33	0.89 (0.59 to 1.34)	168	1.0	49	0.77 (0.56 to 1.07)	69	1.07 (0.80 to 1.42)	.25	.25
NHL (200, 202)	12	0.94 (0.46 to 1.86)	60	1.0	13	0.58 (0.31 to 1.06)	21	0.91 (0.54 to 1.52)	>.50	.42
Hodgkin lymphoma (201)	2	0.42 (0.09 to 2.05)	14	1.0	7	1.71 (0.66 to 4.38)	4	1.30 (0.40 to 4.19)	.08	.06
Multiple myeloma (203)	11	1.79 (0.83 to 3.89)	28	1.0	5	0.46 (0.18 to 1.20)	15	1.28 (0.67 to 2.44)	>.50	>.50
Leukemia (204–207)	7	0.53 (0.23 to 1.21)	63	1.0	24	0.96 (0.60 to 1.56)	29	1.11 (0.70 to 1.74)	.12	.08
Lymphatic leukemia (204)	1	0.24 (0.03 to 1.88)	21	1.0	5	0.57 (0.21 to 1.54)	10	1.02 (0.47 to 2.21)	.46	.41
Myeloid leukemia (205)	4	0.61 (0.20 to 1.91)	26	1.0	8	0.82 (0.36 to 1.83)	10	1.02 (0.48 to 2.16)	>.50	.44
Other and unspecified leukemia (207)	2	0.77 (0.16 to 3.59)	15	1.0	10	1.65 (0.73 to 3.73)	9	1.44 (0.61 to 3.36)	.15	.13
Lymphohematopoietic malignancy of lymphoid origin (200–204)	26	0.94 (0.59 to 1.49)	123	1.0	30	0.65 (0.44 to 0.98)	50	1.06 (0.75 to 1.49)	>.50	>.50
Lymphohematopoietic malignancy of nonlymphoid origin (205, 206, 208, 209)	5	0.69 (0.25 to 1.95)	30	1.0	7	0.61 (0.26 to 1.41)	10	0.86 (0.41 to 1.81)	>.50	>.50

* All calculations used a 2-year lag. ppm = parts per million; RR = relative risk; CI = confidence interval; ICD-8 = *International Classification of Diseases, Eighth Revision*; NHL = non-Hodgkin lymphoma.

† Two-sided likelihood ratio test (1 *df*) of zero slope for continuous formaldehyde exposure among exposed person-years only.

‡ Two-sided likelihood ratio test (1 *df*) of zero slope for continuous formaldehyde exposure among unexposed and exposed person-years.

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

could reflect the increased precision of the relative risk estimates with accrual of additional person-years and myeloid leukemia cases or could reflect a relatively short induction–incubation time for myeloid leukemia because analyses by time since first exposure and first high peak both indicate highest risks within the first 25 years. Our analysis also revealed striking differences in the relative risk for lymphatic and myeloid leukemia for peak exposure, suggesting subtype specificity over the entire cohort follow-up, although this is difficult to reliably assess with mortality data.

Studies of pathologists, embalmers, and other professionals exposed to formaldehyde have provided evidence of increased risk of leukemia in these individuals (11,13,15–18,20,21), with some suggesting an association between work in occupations with formaldehyde exposure and myeloid leukemia (11,13,16). Studies of industrial workers exposed to formaldehyde are less consistent, with some showing positive associations with leukemia (19,22) and others not (23–27). Two cohorts of industrial workers have been recently updated. In a study of 11 039 garment workers in the United States, Pinkerton et al. (19) found a statistically nonsignificant excess of myeloid leukemia that was greatest among workers exposed at earlier time periods, with 10 or more years of exposure and with 20 or more years since first exposure. However, quantitative estimates of peak, average intensity, or cumulative exposure were not developed. The mean TWA8 intensity of 0.15 ppm (range = 0.09–0.20 ppm) reported by Pinkerton et al. (19) for a random sample of study workers in the early 1980s was probably higher than that in the past but considerably lower than in our study. In a study of 14 014 men in British chemical factories similar to those in our study, Coggon et al. (24) showed no association with leukemia or any other lymphohematopoietic malignancy. The authors reported that 28% of workers had estimated exposures >2.0 ppm, suggesting higher exposure levels than those in our study. However, the exposure assessment was not calendar time specific. Because exposure levels have generally decreased over time in most factories, exposures for those working more recently would therefore be classified at higher levels than in our study (8,28). Second, exposure in the Coggon study was evaluated as intensity in the highest exposed job ever held, whereas intensity of exposure in the NCI cohort was based on person–time–weighted average intensity across all jobs. These differences would create the appearance that levels in the British cohort were higher than those in the NCI cohort, when they likely were not. Finally, Marsh and Youk (29) reanalyzed the data from an earlier report of the NCI cohort using different category cut points for average intensity, cumulative exposure, and exposure duration and showed a similar pattern of relative risks as observed by Hauptmann et al. (5) for leukemia and myeloid leukemia. They examined the effect of duration of time worked in each highest peak category and of time since highest peak exposure within each category of peak and the effect of duration and time since first exposure within categories of average

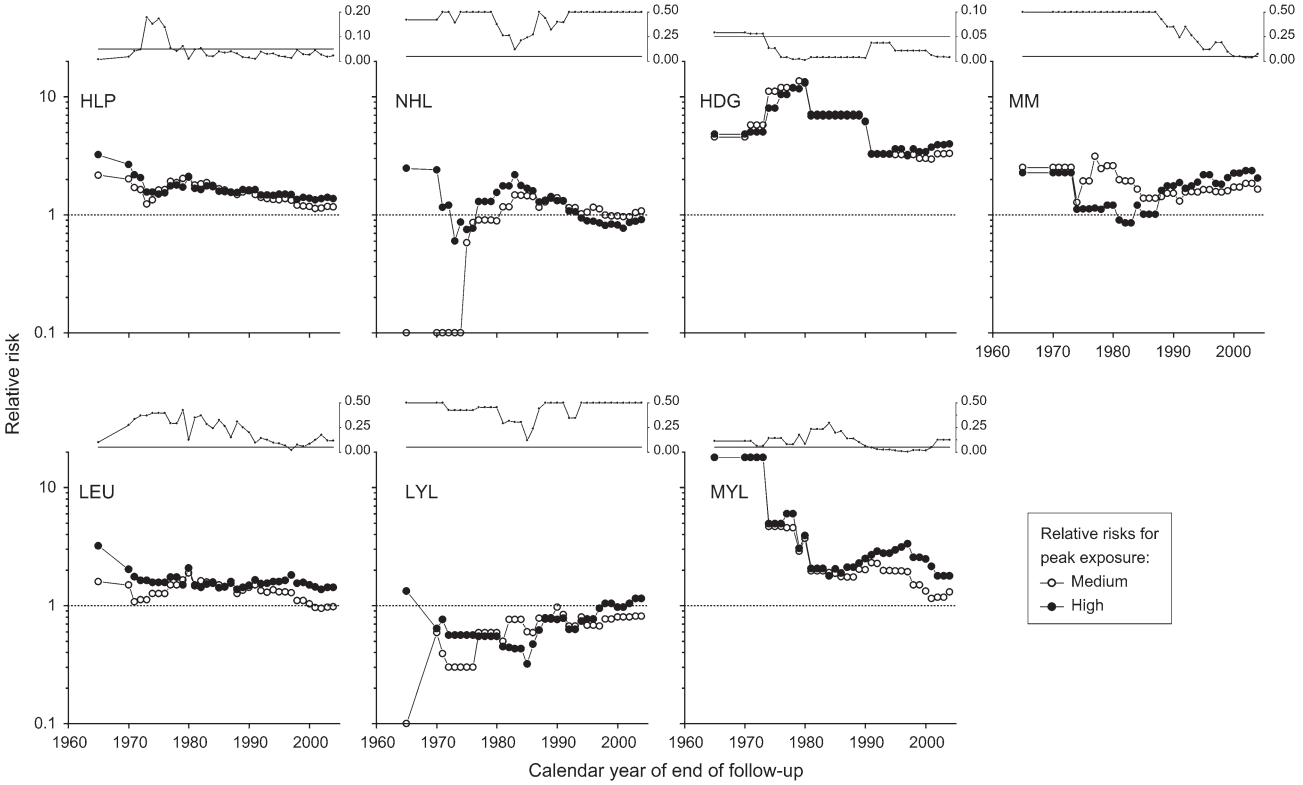

Figure 1. Association between peak formaldehyde exposure and the risk of lymphohematopoietic malignancy. Relative risks for medium-peak (2.0 to <4.0 ppm) and high-peak (≥4.0 ppm) formaldehyde exposure categories compared with the low exposed category (>0 to <2.0 ppm) for lymphohematopoietic malignancies are shown by year of end of follow-up, 1965–2004. Values plotted at 0.1 represent RR = 0 due to no cases in the exposure category; values plotted at 20 represent RR = infinity due to no cases in the referent category. The **small graphs** above the relative risk plots represent the exposure–response trend *P* values based on two-sided likelihood ratio tests (1 *df*) of zero slope for continuous formaldehyde exposure among exposed person-years only. The **points** represent the relative risk estimates based on the cumulative number of cases and person-years accrued from the start of the study to that point in time and for 2004 are equivalent to the relative risk estimates presented in Table 2. HLP = lymphohematopoietic malignancies, NHL = non-Hodgkin lymphoma, HDG = Hodgkin lymphoma, MM = multiple myeloma, LEU = leukemia, LYL = lymphatic leukemia, MYL = myeloid leukemia; RR = relative risk.

intensity of exposure. They found little evidence of associations within exposure categories, which is not unexpected given the limited power for conducting stratified analyses (eg, three categories of time by three categories of exposure based on 28 exposed cases for myeloid leukemia). They also demonstrated that standardized mortality ratios for peak exposure categories and all leukemia and myeloid leukemia increased from deficits in the lowest exposed (eg, 0.4–0.5) to excesses in the highest exposed (eg, 1.2–1.4) categories (29). In our current update through 2004, standardized mortality ratios similarly increased from the lowest to the highest peak exposure categories; however, the standardized mortality ratios in the lowest exposed (referent) category did not statistically significantly differ from 1.0, with values of 0.87 for leukemia and 0.68 for myeloid leukemia.

In its evaluation of the carcinogenicity of formaldehyde, the IARC Working Group concluded that based on available data, it was not possible to identify the mechanism by which formaldehyde may induce leukemia. Although the relevance of cytogenetic damage in mature peripheral lymphocytes to leukemogenesis is unknown (3), the Working Group did note that agents known to cause leukemia in humans also cause chromosomal aberrations in peripheral blood cells of humans. Multiple published studies of humans exposed to inhaled formaldehyde have shown higher rates of chromosomal aberration in peripheral blood lymphocytes in exposed individuals compared with controls (30–41), although the difference was statistically significant only in a subset of these studies (31–38). One study showed an inverse association of chromosomal aberrations with exposure (42).

Excess risks for Hodgkin lymphoma and multiple myeloma also contribute to the association with lymphohematopoietic malignancies overall. Although based on only 27 deaths, the association with Hodgkin lymphoma in our study was strong and includes a statistically significant exposure–response trend for both peak and average exposure. Cumulative risk estimates were greatest in the 1970s, but remained elevated through 2004. Although recent updates of studies of industrial workers by Coggon et al. and Pinkerton et al. showed standardized mortality ratios for Hodgkin lymphoma of 0.70 (95% CI = 0.26 to 1.53) and 0.55 (95% CI = 0.07 to 1.98), respectively (19,24), the strength of the association observed between formaldehyde and Hodgkin lymphoma shown here warrants further study. There are no well-established chemical causes of this disease (43), although there is some evidence that employment in woodworking occupations may increase risk (44,45); the strongest evidence for an etiologic factor for Hodgkin lymphoma may be immune response to childhood infections (43). In our analysis, controlling for wood dust or other industrial coexposures did not substantively change the association.

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

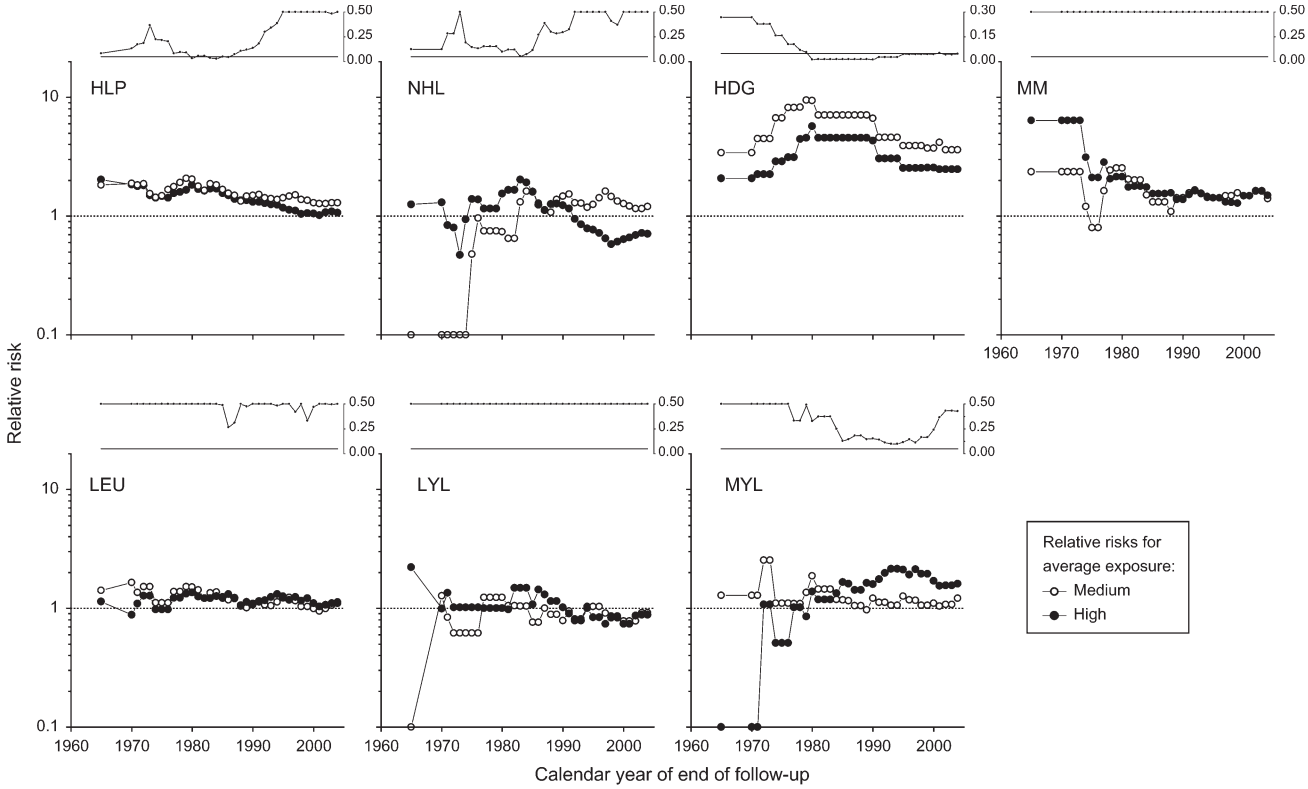

Figure 2. Association between average intensity of formaldehyde exposure and the risk of lymphohematopoietic malignancy. Relative risks for medium (0.5–<1.0 ppm) and high (≥1.0 ppm) average-intensity formaldehyde exposure categories compared with the low exposed category (>0–<0.5 ppm) for lymphohematopoietic malignancies by year of end of follow-up, 1965–2004. Values plotted at 0.1 represent RR = 0 due to no cases in the exposure category. The **small graphs** above the relative risk plots represent the exposure–response trend *P* values based on two-sided likelihood ratio tests (1 *df*) of zero slope for continuous formaldehyde exposure among exposed person-years only. The **points** represent the relative risk estimates based on the cumulative number of cases and person-years accrued from the start of the study to that point in time and for 2004 are equivalent to the relative risk estimates presented in Table 3. HLP = lymphohematopoietic malignancies, NHL = non-Hodgkin lymphoma, HDG = Hodgkin lymphoma, MM = multiple myeloma, LEU = leukemia, LYL = lymphatic leukemia, MYL = myeloid leukemia; RR = relative risk.

Multiple myeloma showed evidence of exposure–response trends for peak exposure within the exposed categories, but the greatest risks occurred among the unexposed. The epidemiological literature regarding formaldehyde and multiple myeloma is limited; Hayes et al. (16) reported a small, non-statistically significant excess among embalmers, but the Pinkerton study found no excess (24).

A limitation of our study is that exposure assessment ceased in 1980. In primary analyses, we assumed that zero exposure occurred after 1980, which may have increased exposure misclassification. Only 11% of the cohort was exposed to formaldehyde in 1980. If exposure continued until age 65, we would have underestimated exposure for 6% of the person-years. Estimated exposure levels in our cohort decreased before 1980 and likely continued to decline for the small numbers exposed after 1980. This pattern of decreasing levels over time is supported by measurement data from OSHA (46) and a study in the wood panel industry (47). Thus, it is unlikely that many workers in the cohort would have had substantial exposures after 1980. When we censored workers still exposed in 1980, risks increased for myeloid leukemia, which may reflect exposure misclassification resulting from assuming zero post-1980 exposure. When we assumed that exposure continued at the same level among the exposed in 1980 until age 65 years, results did not substantively change for any site.

Although exceptional efforts were made to develop high-quality exposure assessments, misclassification undoubtedly occurred. As with all studies, estimation of exposures from limited measurement data is difficult and complex. Although validation was not possible, effects of misclassification may be gauged by comparing full-shift exposure estimates with the monitoring data. A sample of 21 jobs showed a correlation coefficient of 0.50 (8). In a prospective study such as this where information on exposure is assembled independently from, and before, determination of mortality, exposure misclassification would be nondifferential, which would bias relative risks toward the null (48).

We used cause of death information provided by NDI Plus. Although agreement between underlying cause of death on death certificates and hospital diagnoses is generally high, certain types or sites of cancer are underreported on death certificates, including lymphocytic and myeloid leukemia (49). Any misclassification should be nondifferential with respect to exposure. Additionally, we may have underascertained cases because we considered an individual alive if NDI Plus did not identify the subject as deceased. Any resulting underascertainment should have also been nondifferential with respect to exposure. Thus, both possibilities for misclassification would bias our results toward the null.

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

The large size, extended follow-up, and quantitative exposure assessment are major strengths of this study. Despite inherent limitations, the detailed occupational exposure assessment allowed the development of formaldehyde exposure indices not possible in other investigations. Unlike other analyses of cohort studies (19,24,29), we used an internal comparison group to calculate relative risks as opposed to using the general population to calculate standardized mortality ratios. This was a distinct advantage as it reduces the bias that accompanies comparisons between occupational groups and an external referent (50), reduces confounding by unknown factors, and is the most appropriate approach for analyses with quantitative exposure assessments (48). Unexposed and exposed groups may have differed on characteristics such as socioeconomic status; therefore, as in the previous analyses of this cohort (5,6), we used the lowest exposure category as the referent to minimize the impact of unmeasured confounding. We calculated standardized mortality ratios to allow comparison of our results with other studies. Patterns of relative standardized mortality ratios, found by dividing the exposure category–specific standardized mortality ratios by the standardized mortality ratio in the referent (low exposed) category, mirrored those of the relative risk estimates.

The IARC Working Group determined there was "strong, but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde" (3). In the current follow-up, the overall risk of myeloid leukemia has declined from our previous report, but remains somewhat elevated. Although that time trend may suggest that the previous excess risk estimates were due to chance, the pattern is consistent with a possible causal association, with the largest risks occurring closer in time to relevant exposure. The wavelike pattern of the relative risks over time resembles that seen for known leukemogenic agents (51). In addition, the excess risk of lymphohematopoietic malignancies related to peak formaldehyde exposure is partially due to increased risks of multiple myeloma and Hodgkin lymphoma, which were also seen in the earlier follow-up. These associations are more difficult to interpret since, unlike leukemia, they have not been linked to formaldehyde exposure in other epidemiological studies. It is our opinion that the overall pattern of risks seen in this extended follow-up of formaldehyde workers, although not definitive, warrants continued concern. Further studies are needed to evaluate risks of leukemia and lymphatic tumors in other formaldehyde-exposed populations and to assess the biological plausibility of a causal association.

References

1. Bizzari S. *CEH Marketing Report: Formaldehyde*. Palo Alto, CA: SRI International; 2000.
2. Occupational Safety and Health Administration. *Occupational Exposure to Formaldehyde*. OSHA Fact Sheet No. 92–27; Washington, DC: US Department of Labor, Occupational Safety and Health Administration. 1996.
3. International Agency for Research on Cancer (IARC). *Formaldehyde, 2-Butoxyethanol and Propylene Glycol Mono-t-Butyl Ether*. Vol 88. Research Lyon, France: IARC Press; 2006.
4. Blair A, Stewart P, O'Berg M, et al. Mortality among industrial workers exposed to formaldehyde. *J Natl Cancer Inst.* 1986;76(6):1071–1084.
5. Hauptmann M, Lubin J, Stewart P, Hayes R, Blair A. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. *J Natl Cancer Inst.* 2003;95(21):1615–1623.
6. Hauptmann M, Lubin J, Stewart P, Hayes R, Blair A. Mortality from solid cancers among workers in formaldehyde industries. *Am J Epidemiol.* 2004;159(12):1117–1130.
7. Blair A, Stewart P. Correlation between different measures of occupational exposure to formaldehyde. *Am J Epidemiol.* 1990;131(3):510–516.
8. Stewart P, Blair A, Cubit D, et al. Estimating historical exposure to formaldehyde in a retrospective mortality study. *Appl Ind Hyg.* 1986;1(1):34–41.
9. Breslow N, Day N. *The Design and Analysis of Cohort Studies*. Vol 2. Lyon, France: IARC Press; 1987.
10. Preston D, Lubin J, Pierce D, McConney M. *EPICURE*. 2.0. Seattle, WA: Hirosoft International; 1996.
11. Walrath J, Fraumeni J. Mortality patterns among embalmers. *Int J Cancer*. 1983;31(4):407–411.
12. Liebling T, Rosenman K, Pastides H, Griffith R, Lemeshow S. Cancer mortality among workers exposed to formaldehyde. *Am J Ind Med.* 1984;5:423–428.
13. Walrath J, Fraumeni J. Cancer and other causes of death among embalmers. *Cancer Res.* 1984;44(44):4638–4641.
14. Bertazzi P, Pesatori A, Radice L, Zocchetti C, Vai T. Exposure to formaldehyde and cancer mortality in a cohort of workers producing resins. *Scand J Work Environ Health*. 1986(5);12:461–468.
15. Stroup N, Blair A, Erikson G. Brain cancer and other causes of death in anatomists. *J Natl Cancer Inst.* 1986;77(6):1217–1224.
16. Hayes R, Blair A, Stewart P, de Bruyn A, Gerin M. Mortality of U.S. embalmers and funeral directors. *Am J Ind Med.* 1990;18(6):641–652.
17. Hall A, Harrington J, Aw T. Mortality study of British pathologists. *Am J Ind Med.* 1991;20(1):83–89.
18. Levine R, Andjelkovich D, Shaw L. The mortality of Ontario undertakers and a review of formaldehyde-related mortality studies. *J Occup Med.* 1984;26(10):740–746.
19. Pinkerton L, Hein M, Stayner L. Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occup Environ Med.* 2004;61(3):193–200.
20. Milham S. *Occupational Mortality in Washington State, 1950–1979*. Vol 83–116. Cincinnati, OH: DHHS (NIOSH); 1983.
21. Matanoski G. *Risk of Pathologists Exposed to Formaldehyde*. Springfield, VA: National Technical Information Service; 1991.
22. Ott M, Teta M, Greenberg H. Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. *Am J Ind Med.* 1989;16(6):631–643.
23. Hansen J, Olsen J. Formaldehyde and cancer morbidity among male employees in Denmark. *Cancer Causes Control.* 1995;6(4):354–360.
24. Coggon D, Harris E, Poole J, Palmer K. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *J Natl Cancer Inst.* 2003;95(21):1608–1615.
25. Andjelkovich D, Janszen D, Brown M, Richardson R, Miller F. Mortality of iron foundry workers, IV: analysis of a subcohort exposed to formaldehyde. *J Occup Environ Med.* 1995;37(7):826–837.
26. Chiazze L, Watkins D, Fryar C. Historical cohort mortality study of a continuous filament fiberglass manufacturing plant, I: white men. *J Occup Environ Med.* 1997;39(5):432–441.
27. Stellman S, Demers P, Colin D, Boffetta P. Cancer mortality and wood dust exposure among participants in the American Cancer Society Cancer Prevention Study-II (CPS-II). *Am J Ind Med.* 1998;34(3):229–237.
28. Hauptmann M, Lubin J, Stewart P, Hayes R, Blair A. Mortality from solid cancers among workers employed in formaldehyde industries. *Am J Epidemiol.* 2005;161(11):1090–1091.
29. Marsh G, Youk A. Reevaluation of mortality risks from leukemia in the formaldehyde cohort study of the National Cancer Institute. *Regul Toxicol Pharmacol.* 2004;40(2):113–124.
30. Voženíklová H, Tmějová M, Srb V, et al. Environmental and biological monitoring of young people exposed to nonoccupational levels of formaldehyde, toluene and other hydrocarbons. *Proc Fac Med Charles Univ Hradec Kralove.* 1991;34(4):S411–S465.
31. Lazutka J, Lekevicius R, Dedonyté V, et al. Chromosomal aberrations and sister-chromatid exchanges in Lithuanian populations: effects of occupational and environmental exposures. *Mutat Res.* 1999;445(2):225–239.

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011

32. Chebotarev A, Titenko N, Seleznva T, Fomenko V, Katosova L. Comparison of chromosomal aberrations, sister chromatid exchanges and unscheduled DNA synthesis in assessment of the mutagenicity of outside environmental factors. *Tsitol Genet.* 1986;20(2):109–115.
33. Bauchinger M, Schmid E. Cytogenetic effects in lymphocytes of formaldehyde workers of a paper factory. *Mutat Res.* 1985;158(3):195–199.
34. He J, Jin L, Jin H. Detection of cytogenetic effects in peripheral lymphocytes of students exposed to formaldehyde with cytokinesis-blocked micronucleus assay. *Biomed Environ Sci.* 1998;11(1):87–92.
35. Suskov I, Sazonova L. Cytogenetic effects of epoxy, phenolformaldehyde and polyvinylchloride resins in man. *Mutat Res.* 1982;104(1–3):137–140.
36. Dobiáš, Hanzl J, Rössner P, et al. Evaluation of the clastogenic effect of formaldehyde in children in preschool and school facilities. *Cesk Hyg.* 1988;33(10):596–604.
37. Jin F, Zhu R. Cytogenetic effects of formaldehyde on the peripheral blood lymphocytes among industrial workers. *Chin J Ind Hyg.* 1992;10: 277–281.
38. Kitaeva L, Mikheeva E, Shelomova L, Shvartsman P. Genotoxic effect of formaldehyde in somatic human cells in vivo. *Genetika.* 1996;32(9): 1287–1290.
39. Fleig I, Petri N, Stocker W, Thiess A. Cytogenetic analyses of blood lymphocytes or workers exposed to formaldehyde in formaldehyde manufacturing and processing. *J Occup Med.* 1982;24(12):1009–1012.
40. Thomson E, Shackleton S, Harrington J. Chromosome aberrations and sister-chromatid exchange frequencies in pathology staff occupationally exposed to formaldehyde. *Mutat Res.* 1984;141(2):89–93.
41. Vasudeva N, Anand C. Cytogenetic evaluation of medical students exposed to formaldehyde vapor in the gross anatomy dissection laboratory. *J Am Coll Health.* 1996;44(4):177–179.
42. Vargová M, Janota S, Karelová J, Barancokova M, Šulcová M. Analysis of the health risk of occupational exposure to formaldehyde using biological markers. *Analusis.* 1992;20:451–454.
43. Mueller N, Grufferman S. Hodgkin lymphoma. In: Schottenfeld D, Fraumeni J, eds. *Cancer Epidemiology and Prevention*. 3rd ed. New York, NY: Oxford University Press; 2006:872–897.
44. Demers P, Boffetta P. *Cancer Risk From Occupational Exposure to Wood Dust, a Pooled Analysis of an Epidemiological Study*. Vol 30. Lyon, France: IARC Press; 1998.
45. McCunney R. Hodgkin's disease, work and the environment: a review. *J Occup Environ Med.* 1999;41(1):36–46.
46. Occupational Safety and Health Administration. Integrated management information system, 1979–1987. *US Department of Labor.*Washington, DC: US Department of Labor; 1987.
47. Lavoue J, Begin D, Beaudry C, Gerin M. Monte Carlo simulation to reconstruct formaldehyde exposure levels from summary parameters reported in the literature. *Ann Occup Hyg.* 2007;51(2):161–172.
48. Checkoway H, Pearce N, Kriebel D. *Research Methods in Occupational Epidemiology*. Vol 34. 2nd ed. New York, NY: Oxford University Press; 2004.
49. Percy C, Miller B, Ries L. Effect of changes in cancer classification and the accuracy of cancer death certificates on trends in cancer mortality. *Ann N Y Acad Sci.* 1990;609:87–99.
50. Rothman K, Greenland S. *Modern Epidemiology*. Philadelphia, PA: Lippincott, Williams & Wilkins; 1998.
51. Linet M, Devesa SS, Morgan GJ. The leukemias. In: Schottenfeld D, Fraumeni J, eds. *Cancer Epidemiology and Prevention.* 3rd ed. New York, NY: Oxford University Press; 2006:841–871.

Funding

Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health.

Notes

We thank Drs Michael Thun, Elizabeth Fontham, and Noah Seixas for their review and helpful comments. We shared a draft of the manuscript with the participating companies and unions and appreciate their comments. A member of P. A. Stewart's family does consulting work for one of the companies that participated in the study on issues unrelated to formaldehyde exposure.

Present address: Stewart Exposure Assessments, LLC, Arlington, VA (P. A. Stewart).

Present address: Department of Bioinformatics and Statistics, Netherlands Cancer Institute, Amsterdam, the Netherlands (M. Hauptmann).

Manuscript received August 18, 2008; revised March 9, 2009; accepted March 18, 2009.

Downloaded from jnci.oxfordjournals.org by guest on May 25, 2011