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Formaldehyde Exposure and Mortality Risks From Acute Myeloid Leukemia and Other Lymphohematopoietic Malignancies in the US National Cancer Institute Cohort Study of Workers in Formaldehyde Industries

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Objectives: To evaluate associations between cumulative and peak formaldehyde exposure and mortality from acute myeloid leukemia (AML) and other lymphohematopoietic malignancies. **Methods:** Cox proportional hazards analyses. **Results:** Acute myeloid leukemia was unrelated to cumulative exposure. Hodgkin lymphoma relative risk estimates in the highest exposure categories of cumulative and peak exposures were, respectively, 3.76 (P_{trend} = 0.05) and 5.13 (P_{trend} = 0.003). There were suggestive associations with peak exposure observed for chronic myeloid leukemia, albeit based on very small numbers. No other lymphohematopoietic malignancy was associated with either chronic or peak exposure. **Conclusions:** Insofar as there is no prior epidemiologic evidence supporting associations between formaldehyde and either Hodgkin leukemia or chronic myeloid leukemia, any causal interpretations of the observed risk patterns are at most tentative. Findings from this re-analysis do not support the hypothesis that formaldehyde is a cause of AML.

Formaldehyde is environmentally and biologically ubiquitous. Major occupational exposure sources include manufacturing of construction materials, plastics, and garments. Cigarette smoking, consumer products including personal care products and some medications, and ambient air pollution are common nonoccupational sources.[1,2] Formaldehyde is also produced endogenously and is an essential intermediate in the biosynthesis of purines, thymidine, and various amino acids.[3] Thus, formaldehyde is present in small quantities in all body tissues. Exogenous formaldehyde is rapidly metabolized at the site of entry (typically the upper respiratory tract). There is consistent evidence that exogenous formaldehyde cannot reach distant organs including the bone marrow.[4–7]

Cancer risks associated with formaldehyde exposure have been investigated in occupational cohort and community-based case–control studies. The occupational cohort studies generally provide higher-quality evidence than population-based case–control studies—primarily due to better exposure data and a greater potential for higher and more sustained levels of formaldehyde exposure.[8] In 2009, the International Agency for Research on Cancer Working Group concluded that "There is sufficient evidence in humans for the carcinogenicity of formaldehyde. Formaldehyde causes cancer of the nasopharynx and leukaemia."[9(p430)] Baan et al summarized the findings of the Working Group meeting and reported that "The Working Group concluded that, overall, there is sufficient evidence for leukaemia, particularly myeloid leukaemia."[10(p1144)] Despite the clear language regarding causation, the Volume 100F monograph reported that the consensus was based on the small majority of the working group who held the view that the evidence for leukemia was sufficient while a minority of the working group found the evidence for leukemia to be limited. Subsequently, the National Institute of Environmental Health Sciences National Toxicology Program changed the classification of formaldehyde from "anticipated to be carcinogenic in humans" as listed in the Second Report on Carcinogens (RoC) to "known to be a human carcinogen" in the 12th RoC.[11] (Each revision of the RoC is cumulative and includes previous substances as well as newly reviewed substances. The 13th RoC, released in October 2014, contains 243 substance profiles.) The change in classification from anticipated carcinogen to known carcinogen was based on "consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia."[11] Findings from one large cohort mortality study of workers from 10 US plants producing or using formaldehyde [12] have been especially influential in the designation by the International Agency for Research on Cancer[9] and the National Institute of Environmental Health Sciences National Toxicology Program[13] of formaldehyde as leukemogenic. This study was begun by the US National Cancer Institute (NCI) in the 1980s in collaboration with the Formaldehyde Institute, and the first results were published in 1986.[14]

Sequential analyses of updated mortality for the NCI cohort[12,15] reported associations of "peak" exposures with myeloid leukemia (ML) and Hodgkin lymphoma (HL), but not with cumulative, average, or frequency of "peak" exposures. Null or very weak associations were observed with cumulative or "peak" exposures and the other specific lymphohematopoietic malignancies (LHMs) including lymphatic leukemia (LL), non-Hodgkin lymphoma (NHL), and multiple myeloma. Acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) were not reported separately in the NCI analyses but were combined as ML.

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This project was sponsored by the Research Foundation for Health and Environmental Effects (RFHEE), a tax exempt public foundation described in Section 501(c)(3) of the Internal Revenue Code. The sponsor had no role in the design, conduct, analysis, or reporting of results. At the request of the National Research Council (NRC), HC served as a reviewer of the NRC review of the Formaldehyde Assessment, National Toxicology Program 12th Report on Carcinogens. KAM has provided consulting services to Momentive Specialty Chemicals, a producer of formaldehyde, outside the submitted work. KAM, LDD, AEG, and LC are salaried employees of ENVIRON International, a health and environmental consulting firm, that serves various commercial and government clients. No conflicts of interest are declared by PB or by PSJL.

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DOI: 10.1097/JOM.0000000000000466

Although both AML and CML arise in myeloid stem cells, the risk factors associated with AML and CML differ. Most individuals diagnosed with CML have a gene mutation in the leukemia cells called the Philadelphia chromosome, describing the translocation between chromosomes 22 and 9. The translocation leads to the development of the Bcr-Abl oncogene, and this gene instructs the bone marrow to produce Bcr-Abl tyrosine kinase, leading to the development of CML.[16,17] In addition, the known risk factors for AML—tobacco smoking, exposure to benzene, chemotherapy, or radiation treatment—are not recognized risk factors for CML.[17] High-dose radiation, such as that experienced by survivors of atomic bombs or nuclear reactor accidents, is the only recognized environmental risk factor for CML.[17] These recognized differences in histopathology and in the risk factors for AML and CML raise the question of whether the reported association between formaldehyde exposure and combined MLs reflects an underlying association between formaldehyde exposure and the more plausible specific type of leukemia, AML.

We obtained the data included in the most recent update of the NCI cohort[12] via a Technology Transfer Agreement. Our objectives were to replicate the updated findings reported by Beane Freeman et al[12] and to conduct additional analysis of associations of specific LHM, and especially AML, with peak exposure, using an alternative, more standard definition of peak.

METHODS

We performed analyses to replicate findings reported in the most recent follow-up of the cohort,[12] including the descriptive characteristics of the cohort—the number of workers, person-time, median length of follow-up, race, sex, pay category, the number of deaths, and median age at entry and exit from the study. We also replicated the reported number of workers never exposed to formaldehyde, median and range for estimated formaldehyde 8-hour time-weighted average (TWA8) exposures, cumulative exposure, the number of workers with average intensity levels 1.0 ppm or more, and the number of workers who experienced peak formaldehyde exposures 4.0 ppm or more. Cause-specific mortality among the cohort was compared with race- and sex-specific national mortality rates by age and calendar interval for cause-specific categories of death from the National Institute for Occupational Safety and Health (NIOSH, Atlanta, GA) by computing standardized mortality ratios (SMRs).[18,19] Rates for lymphatic leukemia, ML, AML, and CML were not available through NIOSH and were instead obtained from the Surveillance Epidemiology and End Results Cancer Query Systems (CanQues).[20] The final replication included exposure–response analyses for cumulative, average, and peak exposures with mortality for LHM, using the same exposure metrics defined by Stewart et al.[21] and mortality outcome categories as reported in Beane Freeman et al.[12] Only trivial differences were found.

In the original analysis, peak exposures were defined as estimates of "short-term exposures (generally less than 15 minutes) that exceeded the TWA8 category".[12,21] Workers in jobs not identified as having peak exposure levels that exceeded the TWA8 category were assigned the TWA8 intensity category as their peak exposure. Thus, peaks were defined on a worker-specific relative basis. Moreover, neither frequency nor duration of peaks had been included in the definition of the peak exposure metric previously (eg, at least 1 year of employment in jobs likely experiencing more than 4 ppm exposure for 15 to 60 minutes at least weekly). For our reanalyses, we redefined peak exposures on an absolute scale, that is, at least 1 continuous month of employment in jobs identified in the original exposure characterization as likely having short-term exposure excursions of 2 ppm or more to less than 4 ppm or 4 ppm or more on a weekly or daily basis.[21] Our definition of peak exposure did not include employment in jobs likely experiencing (1) short-term excursions more than 0 ppm and less than 2 ppm; (2) short-term excursions identified as occurring as frequently as hourly; and (3) short-term excursions identified as occurring as infrequently as monthly.

We applied Cox proportional hazards models to estimate exposure–response relations for both cumulative and the newly derived absolute peak exposures (Stata Statistical Software, College Station, TX). These methods produce statistically similar results to Poisson regression,[22] and both methods can accommodate time-dependent treatment of exposure variables. Replication of previous results allowed us to extend our analysis to examine the robustness of previously observed associations between peak exposure (as originally defined) and mortality from specific LHMs, including subtypes of leukemia as well as original analyses of AML and CML risk.

Peak exposure was treated in a time-dependent manner such that subjects accrued person-time in the non–peak exposure category until the start of their first peak exposure job, after which they accrued person-time in that specific peak exposure category. Because of the time-varying nature of peak exposure, in which study subjects may also transfer from job assignments with peak exposures to subsequent job assignments without peak exposures, we also conducted a sensitivity analysis to evaluate duration of time in jobs with short-term excursions 2 ppm or more.

Cumulative formaldehyde exposure was modeled categorically, with cut points based on approximate quartiles of exposure (rounded to the nearest half fraction) for the full cohort. Because of the small number of HL ($n = 5$) and subtypes of ML deaths ($n = 4$ AML and $n = 2$ CML) in the lowest exposure quartile (ie, less than 0.05 ppm-years), the first two quartiles of exposure were combined to form a new referent category (less than 0.5 ppm-years). Cumulative exposure was also treated in a time-dependent manner, with exposure accruing on a yearly basis.

We did not conduct analyses according to average exposure intensity because the previous findings for ML with respect to average intensity were unremarkable (as were the findings for cumulative exposure). Moreover, cumulative exposure is the conventional exposure metric used for risk assessment of chronic diseases, such as cancer, and the default policy for regulatory quantitative risk assessment assumes proportionality of cancer risk with cumulative exposure. Average exposure intensity is also correlated with cumulative exposure, which is the sum of average intensity in job times duration in job over all jobs in an employee's work history.

All Cox models of peak and cumulative exposures used attained age as the time scale and controlled for sex, race (white or other), and pay category (salary, ever wage, or unknown).

Analyses were conducted for NHL, chronic lymphocytic leukemia (CLL), HL, multiple myeloma, ML, AML, and CML, and combining all leukemias. We included CLL in the NHL grouping because CLL has been classified as NHL since 2001.[23,24]

On the basis of observations of workers exposed to high concentrations of benzene, AMLs are expected to occur within 10 or at most 15 years since first exposure.[25–27] Therefore, peak exposures occurring up to 10 years preceding death would be particularly relevant for AML etiology. We also performed separate Cox models to lag exposure by 1, 2, or 5 years to allow for disease latency intervals. These analyses were conducted for the entire cohort and separately for the subset of 16,306 employed for 1 year or more to eliminate possible confounding by unmeasured risk factors or underlying health and risk differences associated with short-term employment. A disproportionate number of HL and AML deaths in the reference group was lost when the analyses were restricted to cohort members employed at least 1 year—five of nine HLs (56%) and 11 of 17 AMLs (65%) were lost in the cumulative exposure analysis; and 7 of 15 HLs (47%) and 9 of 21 AMLs (43%) were lost in the peak exposure analysis. To stabilize the referent group, we combined the first two quartiles of exposure into a new referent category.

Because job histories were available only through 1980, exposure histories were incomplete for the 3434 persons (13.4%) known

to have worked after that date. In addition, no information was available on formaldehyde exposure for any work history before entry into the cohort or subsequent to leaving the industry. We performed sensitivity analyses by separately analyzing survival for the study subjects with complete work history and ending follow-up in 1985 and by assigning exposure of the most recent job until the age of 65 years or the end of follow-up for those with truncated work history.

We also performed separate sensitivity analyses in which we assumed that all 21 deaths coded as "acute leukemia, NOS" (ICD-8 207.0) were either AML deaths or ALL deaths, as well as analyses that evaluated time since first exposure to formaldehyde and time since first exposure to peak 4 ppm or more, consistent with results reported in the online supplementary tables by Beane Freeman et al.[12] Only four deaths were reported as "chronic leukemia, unspecified" on death certificates (compared with 13 CMLs and 32 CLLs), and therefore we did not conduct additional analyses reclassifying these into assumed specific categories.

RESULTS

Descriptive features of the full cohort, the subset employed 1 year or more, and the subset employed less than 1 year are summarized in Table 1.

A total of 25,619 formaldehyde workers were followed from year of first employment at the facility (1930 to 1966) or year of cohort identification (1934 to 1958), whichever was later, through death, loss-to-follow-up, or December 31, 2004, whichever was earliest. We calculated 997,514 person-years compared with 998,106 as reported by Beane Freeman et al.[12] Of the total 25,619 workers, 3478 (13.6%) worked in jobs with peaks 2 ppm or more to less than 4 ppm, and 2907 (11.3%) had jobs with peaks 4 ppm or more.

TABLE 1. Descriptive Statistics Comparing the Full Cohort ($n = 25{,}619$) and Workers Employed for 1 Year or Longer ($n = 16{,}306$)

Variable	Full Cohort ($n = 25{,}619$)	Workers Employed 1 Yr or More ($n = 16{,}306$)	Workers Employed Less Than 1 Yr ($n = 9{,}313$)
Race (%)			
White	23,758 (92.7)	15,148 (92.9)	8,610 (92.5)
Nonwhite	1,861 (7.3)	1,158 (7.1)	703 (7.6)
Sex (%)			
Male	22,493 (87.8)	14,310 (87.8)	8,183 (87.9)
Female	3,126 (12.2)	1,996 (12.2)	1,130 (12.1)
Pay status (%)			
Hourly	20,116 (78.5)	11,970 (73.4)	8,146 (87.5)
Salaried	4,600 (18.0)	3,948 (24.2)	652 (7.0)
Unknown	903 (3.5)	388 (2.4)	515 (5.5)
Duration of follow-up, yrs			
Mean (standard deviation)	38.9 (13.9)	39.0 (13.2)	38.8 (15.0)
Median (range)	41.8 (0.1–66.9)	41.8 (0.1–66.9)	41.8 (0.1–65.2)
25th percentile	31.8	31.9	31.6
75th percentile	48.5	47.9	49.4
Duration of employment, yrs			
Mean (standard deviation)	9.0 (11.3)	13.9 (11.5)	0.4 (0.3)
Median (range)	2.6 (>0.0–47.6)	11.1 (1.0–47.6)	0.3 (>0.0–<1.0)
25th percentile	0.5	3.1	0.2
75th percentile	16.5	23.5	0.6
Age at start of follow-up, yrs			
Mean (standard deviation)	29.1 (10.2)	30.4 (10.5)	26.8 (9.1)
Median (range)	26.0 (8.1–82.7)	27.7 (8.1–82.7)	23.7 (15.2–82.6)
25th percentile	21.1	22.1	20.0
75th percentile	34.9	37.0	30.9
Age at end of follow-up, yrs			
Mean (standard deviation)	68.0 (13.3)	69.5 (12.4)	65.6 (14.4)
Median (range)	69.3 (15.3–102.0)	70.5 (17.4–102.0)	67.2 (15.3–102.0)
25th percentile	61.6	62.7	59.8
75th percentile	76.9	77.9	75.2
Cumulative exposure, ppm-yr			
Mean (standard deviation)	3.2 (8.4)	4.9 (10.1)	0.2 (0.3)
Median (range)	0.4 (0.0–107.5)	1.4 (0.0–107.5)	0.1 (0.0–3.4)
25th percentile	0.04	0.3	0.01
75th percentile	2.4	5.0	0.2
Peaks (%)			
≥2–<4 ppm peak	3,478 (13.6)	2,712 (16.6)	766 (8.2)
≥4 ppm peak	2,907 (11.3)	2,631 (16.1)	276 (3.0)
Study subjects with complete work history (%)	22,185 (86.6)	12,872 (78.9)	9,313 (100.0)

We replicated closely the SMR findings reported in the original analysis and added analyses for AML and CML separately (Table 2). When all deaths from "Acute Leukemia, NOS" were assumed to be AML, the AML SMRs increased from 0.80 (95% confidence interval [CI], 0.56 to 1.14, based on 30 deaths) to 0.94 (95% CI, 0.71 to 1.25 based on 49 deaths) for the formaldehyde-exposed group and from 0.93 (95% CI, 0.25 to 2.37, based on four deaths) to 1.00 (95% CI, 0.45 to 2.23, based on six deaths) for the group not exposed to formaldehyde (results not shown). Thus, the deficit of AMLs is unlikely due to ambiguous coding of acute leukemia deaths.

All Leukemias

No association between cumulative formaldehyde exposure and mortality from all leukemias combined was observed for the entire cohort (Table 3).

Nevertheless, risks were elevated among those employed for 1 year or more, regardless of cumulative exposure category, due to the large loss of leukemia cases in the referent group (27 cases worked less than 1 year)—hazard ratio (HR) = 2.44; 95% CI, 1.08 to 5.51 for those with cumulative exposures of 0.5 to less than 2.5 ppm-years and HR = 2.49; 95% CI, 1.13 to 5.49 for those with 2.5 ppm-years or more ($P_{trend} = 0.04$; Table 3).Peak exposures 2.0 ppm or more to less than 4 ppm (HR = 2.23; 95% CI, 1.34 to 3.72) and 4.0 ppm or more (HR = 2.07; 95% CI, 1.22 to 3.49) were associated with all leukemias, and similar associations were seen among those employed for 1 year or more (HR = 2.46; 95% CI, 1.29 to 4.67 and HR = 2.45; 95% CI, 1.32 to 4.52, respectively) (Table 4).

Myeloid Leukemias

Myeloid leukemia (all types combined) was not associated with cumulative formaldehyde exposure in the entire cohort. There was, however, a modest, but not statistically significant, association of cumulative exposure and ML among workers employed 1 year or more (Table 3). Peak exposure of 2.0 ppm or more to less than 4 ppm was associated with ML in the full cohort (HR = 2.09; 95% CI, 1.03 to 4.26) and similarly among those employed 1 year or more (HR = 2.49; 95% CI, 1.01 to 6.15) (Table 4). HRs for peaks of 4.0 ppm or more were weaker, but still elevated, and trends were not statistically significant (ie, $P_{trend} = 0.06$ and 0.08, respectively).

CML and AML

The association seen with peak exposure and ML was examined by specific subtype of ML, that is, AML and CML; however, numbers were small, and therefore HR estimates were imprecise. HR estimates for CML among the full cohort were elevated for peak exposure 2.0 ppm or more to less than 4.0 ppm (HR = 2.62; 95% CI, 0.64 to 10.66) and 4.0 ppm or more (HR = 3.07; 95% CI, 0.83 to 11.40). For AML, risk estimates were considerably lower and did not increase at the highest peak formaldehyde levels. The AML findings were only minimally changed when 21 deaths from "acute leukemia, NOS" all were assumed to be AML.

Analysis of time since first and time since last peak exposure revealed that, among the 13 of 34 AML deaths in the full cohort with peak exposures more than 2.0 ppm, only four worked in jobs with peaks within the 20 years preceding death, and only one occurred (similar to expected) within the typical AML latency window of 2 to 15 years.

Hodgkin Lymphoma

Of the LHMs, HL was most strongly and consistently associated with both cumulative (Table 3) and peak (Table 4) formaldehyde exposures. For the full cohort, the HRs for HL were 2.52 (95% CI, 0.93 to 6.83) and 3.11 (95% CI, 1.16 to 8.34) for cumulative exposure 0.5 to less than 2.5 ppm-years and 2.5 ppm-years or more, respectively; HR estimates (95% CI) for peak exposure categories were 2.18 (0.77 to 6.19) and 3.38 (1.30 to 8.81), respectively, for peak categories 2 ppm or more to less than 4 ppm and 4 ppm or more, respectively. Similar results were observed for workers employed for 1 year or more.

Other LHMs

None of the other LHMs was associated with either cumulative or peak exposure (Tables 3 and 4).

The results presented in Tables 3 and 4 were not materially different when we applied exposure lags (1, 2, or 5 years), adjusted for total employment duration, adjusted for exposure confidence score,[21] or when follow-up was truncated as of 1985 (ie, limiting the exposure to the years for which work history/exposure data were available) (results not presented but available on request). Results were only minimally changed when we restricted analyses to cohort members with complete work histories and ended follow-up in 1985, or when we assigned people with incomplete work/exposure history to the exposure of their final job until the age of 65 years or end of follow-up (results not presented but available on request).

DISCUSSION

The NCI study of occupational formaldehyde exposure has been influential in the recent classification of formaldehyde as a human leukemogen. The primary objectives of our reanalyses of these data were to determine the robustness of the findings to alternative exposure classification schemes, especially for peak exposures, and to evaluate whether formaldehyde exposure metrics were associated specifically with AML mortality. In the original analysis conducted by the NCI investigators, peak was defined on a relative basis, with respect to individual workers' exposure histories. This approach to defining peaks complicates data interpretation and risk assessments that are ultimately applied to set occupational and environmental exposure standards. The alternative approach that we applied defined peaks in terms of absolute exposure intensity and duration and also treated peaks as a time-varying exposure. This approach is a decided strength of the re-analysis because it permits direct comparisons among similar studies and is applicable to risk assessment. As for formaldehyde exposure and AML mortality, no results specific to AML—the type of leukemia most plausibly related to chemical exposures—had been presented in any of the previous publications on this cohort.

One general limitation of the data from this cohort is that job assignments were not documented beyond the initial study end date; thus, exposures could not be estimated for years worked after 1980. To overcome this limitation, Beane Freeman et al[12] performed sensitivity analyses to evaluate the effect of unknown exposures after 1980. We also evaluated the effect of unknown exposure by assuming that exposure continued in the last assigned job held until the age of 65 years, death, or end of follow-up. We also analyzed mortality for the cohort members with complete work history records and ending follow-up as of 1985. None of these approaches generated different results, suggesting that exposures in later years, which would be expected to be low relative to earlier years, were not determinants of mortality risks.

Another inherent limitation of this study is that despite its large overall size and nearly 1 million person-years of follow-up, there is a relatively small number of AML deaths observed among individuals employed for more than 1 year and most highly exposed to formaldehyde. Acute myeloid leukemia is the specific ML plausibly associated with chemical risk factors, such as benzene[9] and antineoplastic agents.[28] Furthermore, few of the employees who died of AML had any peak exposures (as originally defined or as we redefined it here), and nearly none had peak exposures within a reasonable time window of latency. For this reason, extending follow-up of mortality will not be helpful for shedding light on AML associations with peak exposure because the cohort is now 35 years since

TABLE 2. Replication of Mortality From Lymphohematopoietic Malignancies Among a Cohort of US Workers Nonexposed and Exposed to Formaldehyde, Follow-Up Through 2004

	Beane Freeman et al (2009)[12]*				Current Analysis 2014†			
	Nonexposed ($n = 3,108$)		Exposed ($n = 22,511$)		Nonexposed ($n = 3,136$)		Exposed ($n = 22,483$)	
Cause of Death (ICD-8 Codes)	**Observation**	**SMR (95% CI)**	**Observation**	**SMR (95% CI)**	**Observation**	**SMR (95% CI)**	**Observation**	**SMR (95% CI)**
Lymphohematopoietic malignancies (200–209)†	33	0.86 (0.61–1.21)	286	0.94 (0.84–1.06)	NC†	—	NC†	—
NHL (200, 202)‡	12	0.86 (0.49–1.52)	94	0.85 (0.70–1.05)	12	0.90 (0.51–1.59)	94	0.83 (0.68–1.01)
Hodgkin disease (201)	2	0.70 (0.17–2.80)	25	1.42 (0.96–2.10)	2	1.04 (0.13–3.74)	25	1.34 (0.91–1.99)
Multiple myeloma (203)	11	1.78 (0.99–3.22)	48	0.94 (0.71–1.25)	11	1.82 (1.01–3.29)	48	0.93 (0.70–1.24)
Leukemia (204–207)	7	0.48 (0.23–1.01)	116	1.02 (0.85–1.22)	7	0.53 (0.25–1.12)	116	1.01 (0.84–1.21)
Lymphatic leukemia (204)§	1	0.26 (0.04–1.82)	36	1.15 (0.83–1.59)	1	0.28 (0.01–1.57)	36	1.14 (0.82–1.57)
Myeloid leukemia (205)§	4	0.65 (0.25–1.74)	44	0.90 (0.67–1.21)	4	0.69 (0.19–1.76)	44	0.86 (0.64–1.16)
AML (205.0)§	NR	—	NR	—	4	0.93 (0.25–2.37)	30	0.80 (0.56–1.14)
CML (205.1)§	NR	—	NR	—	0	—	13	0.97 (0.56–1.67)

*US rates obtained from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) (personal correspondence, Dr Beane Freeman, October 22, 2013).

†US age-, sex-, race-, and calendar-specific mortality rates, 1960 to 2007 obtained from NIOSH. 1960 rates were applied to earlier years. NIOSH rates for ICD-8 204, 205, 208, and 209 were not provided separately. ICD-8 208 is included with other benign and unspecified nature neoplasms. ICD-8 209 is included with all other disease of blood forming organs.

‡The NIOSH rate for NHL also includes ICD, 8th revision, code 275.5.

§SEER CanQues US mortality rates for 1970 to 2009 were used in the Current Analysis (2014) for LL, ML, AML, and CML. 1970 rates were applied to earlier years. Nonwhite workers in the data set were compared with rates for blacks from SEER US mortality rates. The myeloid leukemia rate is the sum of the AML and CML rates. One death was coded to ICD-8 205.9, unspecified myeloid leukemia. Other and unspecified myeloid leukemias are not included in the rate because SEER only provides a combined "other myeloid/monocytic leukemia" category.

AML, acute myeloid leukemia; CI, confidence interval; CML, chronic myeloid leukemia; ICD-8, International Classification of Diseases, 8th Revision; NC, not calculated; NHL, non-Hodgkin lymphoma; SMR, standardized mortality ratio.

TABLE 3. Association Between Cumulative Exposure to Formaldehyde and Death From Lymphohematopoietic Malignancies, Mortality Follow-Up Through 2004

Category of Death (ICD-8 Codes)		Full Cohort (n = 25,619)	Worked ≥1 Yr (n = 16,306)	
Cumulative Exposure (ppm-yr)	No. of Deaths	HR† (95% CI)	No. of Deaths	HR† (95% CI)
NHL (200, 202, 204.1)				
0–<0.5	68	1.0 (referent)	33	1.0 (referent)
0.5–<2.5	33	0.96 (0.63–1.46)	27	0.79 (0.47–1.32)
≥2.5	37	0.77 (0.51–1.16)	37	0.65 (0.40–1.07)
P trend		0.22		0.09
CLL (204.1)				
0–<0. 5	14	1.0 (referent)	6	1.0 (referent)
0.5–<2.5	9	1.21 (0.52–2.81)	6	0.93 (0.29–2.96)
≥2.5	9	0.82 (0.35–1.93)	9	0.81 (0.28–2.37)
P trend		0.69		0.69
Hodgkin lymphoma (201)				
0–<0.5	9	1.0 (referent)	4	1.0 (referent)
0.5–<2.5	8	2.52 (0.93–6.83)	6	2.46 (0.63–9.55)
≥2.5	10	3.11 (1.16–8.34)	10	3.76 (0.99–14.26)
P trend		0.02		0.05
Multiple myeloma (203)				
0–<0.5	34	1.0 (referent)	19	1.0 (referent)
0.5–<2.5	6	0.37 (0.16–0.90)	5	0.27 (0.10–0.74)
≥2.5	19	0.88 (0.49–1.58)	19	0.65 (0.33–1.28)
P trend		0.51		0.29
All leukemia (204–207, excluding 204.1)				
0–<0.5	36	1.0 (referent)	9	1.0 (referent)
0.5–<2.5	23	1.27 (0.75–2.15)	20	2.44 (1.08–5.51)
≥2.5	32	1.29 (0.79–2.10)	32	2.49 (1.13–5.49)
P trend		0.30		0.04
Myeloid leukemia (205)				
0–<0.5	23	1.0 (referent)	7	1.0 (referent)
0.5–<2.5	11	0.98 (0.47–2.03)	9*	1.53 (0.54–4.27)
≥2.5	14	0.94 (0.47–1.86)	14	1.58 (0.59–4.23)
P trend		0.85		0.39
AML (205.0)				
0-<0.5	17	1.0 (referent)	6	1.0 (referent)
0.5-<2.5	7	0.87 (0.36–2.12)	6	1.16 (0.36–3.76)
≥2.5	10	0.96 (0.43–2.16)	10	1.31 (0.44–3.95)
P trend		0.90		0.63
CML (205.1)				
0–<0.5	6	1.0 (referent)	1	1.0 (referent)
0.5–<2.5	3	0.97 (0.24–3.93)	2	2.91 (0.24–35.64)
≥2.5	4	0.92 (0.25–3.36)	4	3.81 (0.36–40.44)
P trend		0.90		0.27

*Includes one death from myeloid leukemia, not specified as acute or chronic.

†Cox proportional hazards model using attained age as the time scale variable, adjusted for sex, race (white or other), and pay category (salary, ever wage, or unknown). Results were comparable to the original results based on the Poisson regression models for specific LHMs, and we additionally conducted specific analyses for AML and CML. Minor differences remaining between results can be attributed to some methodological refinements as well as rounding error (eg, we were only provided data on month rather than exact dates of employment changes).

AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HR, hazard ratio; ICD-8, International Classification of Diseases, 8th Revision; NHL, non-Hodgkin lymphoma.

last known peak exposure, and AMLs increase sharply with older age, independent of exposure. We also explored the 21 deaths identified as "acute leukemia, unspecified" on death certificates; these likely represent some unknown combination of AML and ALL diagnoses (only three ALLs were reported on death certificates, with 5.8 expected, suggesting that ALLs were underreported).

Our HL results, similar to previous reports on this cohort, identified a slight overall excess of HL deaths among exposed workers (Table 2). Five of nine HL deaths in the referent group had worked less than 1 year (Table 3). Furthermore, our reanalyses confirmed associations between different exposure metrics (cumulative and peak) to formaldehyde and HL. Interpretation of the HL

TABLE 4. Association Between Peak (ie, Short-Term Excursions 2 ppm or More to Less Than 4 ppm and 4 ppm or More)* Not Lagged And Death From Lymphohematopoietic Malignancies, Mortality Follow-Up Through 2004

		Full Cohort ($n = 25,619$)	Worked ≥1 year ($n = 16,306$)	
Category of Death (ICD-8 Codes) Peak Exposure	**No. of Deaths**	**HR† (95% CI)**	**No. of Deaths**	**HR† (95% CI)**
NHL (200, 202, 204.1)				
No peak‡	98	1.0 (referent)	63	1.0 (referent)
≥ 2.0–<4 ppm	19	0.94 (0.58–1.55)	16	0.93 (0.53–1.61)
≥4 ppm	21	0.98 (0.60–1.58)	18	0.89 (0.52–1.52)
P trend		0.88		0.65
CLL (204.1)				
No peak‡	23	1.0 (referent)	13	1.0 (referent)
≥2.0–<4 ppm	4	0.79 (0.27–2.30)	4	1.07 (0.35–3.32)
≥4 ppm	5	0.95 (0.36–2.52)	4	0.91 (0.29–2.83)
P trend		0.82		0.90
Hodgkin lymphoma (201)				
No peak‡	15	1.0 (referent)	8	1.0 (referent)
≥2.0–<4 ppm	5	2.18 (0.77–6.19)	5	3.50 (1.06–11.56)
≥4 ppm	7	3.38 (1.30–8.81)	7	5.13 (1.67–15.77)
P trend		0.01		0.003
Multiple myeloma (203)				
No peak‡	43	1.0 (referent)	28	1.0 (referent)
≥2.0–<4 ppm	8	0.99 (0.46–2.13)	7	0.98 (0.43–2.28)
≥4 ppm	8	0.95 (0.44–2.06)	8	0.97 (0.43–2.16)
P trend		0.90		0.94
All leukemia (204–207, excluding 204.1)				
No peak‡	48	1.0 (referent)	26	1.0 (referent)
≥2.0–<4 ppm	22	2.23 (1.34–3.72)	16	2.46 (1.29–4.67)
≥4 ppm	21	2.07 (1.22–3.49)	19	2.45 (1.32–4.52)
P trend		0.001		0.002
Myeloid leukemia (205)				
No peak‡	27	1.0 (referent)	14	1.0 (referent)
≥2.0–<4 ppm	11	2.09 (1.03–4.26)	8	2.49 (1.01–6.15)
≥4 ppm	10	1.80 (0.85–3.79)	8	2.03 (0.82–5.03)
P trend		0.06		0.08
AML (205.0)				
No peak‡	21	1.0 (referent)	12	1.0 (referent)
≥2.0–<4 ppm	7	1.71 (0.72–4.07)	5	1.78 (0.61–5.25)
≥4 ppm	6	1.43 (0.56–3.63)	5	1.51 (0.51–4.44)
P trend		0.31		0.37
CML (205.1)				
No peak‡	6	1.0 (referent)	2	1.0 (referent)
≥2.0–<4 ppm	3	2.62 (0.64–10.66)	2	4.83 (0.64–36.42)
≥4 ppm	4	3.07 (0.83–11.40)	3	5.32 (0.81–34.90)
P trend		0.07		0.07

*1 month or more continuous exposure.

†Attained age as the time scale variable, adjusted for sex, race (white or other), and pay category (salary, ever wage, or unknown).

‡Referent group includes study subjects with peaks less than 2 ppm of hourly, daily, weekly, and monthly frequency as well as peaks 2 ppm or more if hourly or monthly frequency.

AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HR, hazard ratio; ICD-8, International Classification of Diseases, 8th Revision; NHL, non-Hodgkin lymphoma.

findings is complicated because there is little epidemiologic support for chemical exposures in the etiology of HL. In particular, increased risk of HL has not been observed in other occupational studies of formaldehyde-exposed cohorts. Coggon et al[29] reported an SMR of 0.70 (95% CI, 0.26 to 1.53) based on six deaths during 1940 to 2000 among more than 14,000 men employed after 1937 in the UK formaldehyde industry. Although follow-up was extended through 2012 in the UK cohort, results were not presented for HL.[30] No increased risk of HL was observed in a recent update of more than 11,000 garment workers followed for mortality from the mid-1950s to 2008 based on four deaths (SMR = 0.95; 95% CI, 0.26 to 2.44).[31]

Hodgkin leukemia is heterogeneous with respect to age at diagnosis and histology. The incidence of HL is described by a bivariate distribution in which incidence increases and peaks between the ages of 20 to 29 years, decreases between the ages of 30 to 54 years, and then increases again after the age of 55 years.[32,33] Little is known about risk factors for specific subtypes of HL. Furthermore, the deaths were classified according to the International Classification of Diseases, Eighth Revision, in the database, which does not allow investigation of specific subtypes of HL.

Overall, the absence of increased risks in other occupational cohorts and the lack of a plausible biological mechanism for chemical exposures in the etiology of HL detract from a causal explanation for the observed association in this study. The small numbers of HL deaths increase the likelihood that random error contributed to the observed patterns.

For ML, initial Cox proportional hazards analyses suggested an association of similar magnitude for both categories of peak exposure (ie, 2 ppm or more to less than 4 ppm and 4 ppm or more in separate analyses compared with the same "no peaks" referent). Nevertheless, among the MLs, a stronger association with peak exposure was seen for CML than for AML. The clear lack of an association with cumulative exposure, the default dose metric in most epidemiologic studies, for both CML and AML further weakens arguments for causal attribution. Moreover, and in contrast to HL, there is no indication of an excess mortality due to AML in this cohort, even after assuming that all 21 "unspecified" acute leukemias were AMLs. Our SMR analysis confirmed a deficit of MLs of more than 30% among the unexposed, but only a small deficit of AML among the unexposed. In contrast, 13 deaths from CML were observed among the exposed group (compared with approximately 13 expected), and 30 AMLs were observed among the exposed group (compared with approximately 38 expected) (Table 2). It is possible that there may be some underlying differences between the nonexposed and exposed subcohorts, such that a deficit of MLs among the nonexposed gave rise to an apparent association in analysis using an internal referent. Many of the LHM deaths occurred among the short-term workers, who might have had the least opportunity to accumulate exposure, and were half as likely to have worked in jobs classified as having peak exposures. Conversely, workers who remain unexposed over their entire duration of employment were more likely to have worked as technicians or white-collar employees rather than as production workers or laborers, and differences in results between the two groups may reflect socioeconomic differences. Other studies have shown increased risks of AML of similar magnitude among professionals, including groups unexposed to formaldehyde or any chemicals, such as priests (Standardized Incidence Ratio = 1.75; 95% CI, 1.20 to 2.47).[34]

Other cohorts of formaldehyde-exposed workers have not demonstrated notable associations with ML. In the original analyses of the British cohort, Coggon et al[29] reported no excess of leukemia deaths overall (SMR = 0.91; 95% CI, 0.47 to 1.59) or among the subcohort with high formaldehyde exposure (SMR = 0.71; 95% CI, 0.31 to 1.39) estimated from limited exposure monitoring data and worker reports of irritant symptoms; however, results for ML or its subtypes AML and CML were not provided. The most recent update of that cohort[30] also reported no excess of leukemia deaths overall (SMR = 1.02; 95% CI, 0.77 to 1.33) or among the high formaldehyde exposure subcohort (SMR = 0.82; 95% CI, 0.44 to 1.41). Analyses of ML deaths were similar for the total cohort (SMR = 1.2; 95% CI, 0.84 to 1.66) and for the high formaldehyde exposure subcohort (SMR = 0.93; 95% CI, 0.40 to 1.82); however, results for AML deaths were not presented. No associations with any of the other LHM were observed among the total cohort or among the high formaldehyde exposure group. The US NIOSH garment workers cohort had suggested an association between formaldehyde and leukemia; however, the authors recently reported that the extended follow-up of this cohort "did not strengthen previously observed associations."[31] The interpretation of results of extended follow-up of all of these cohorts becomes more complicated, however, as background rates of AML increase 30-fold from aged 50 to 59 years to 80 years and older,[33] and these are less likely to be related to workplace exposures from decades earlier.

Leukemias have shorter latencies than solid tumors, which often manifest 20 or more years after exposure. Studies of atomic bomb survivors in Japan found that AML incidence peaks between 5 and 7 years after radiation exposure and declines over time.[35,36] Deschler and Lubbert[37] reported that the incidence of AML following chemotherapy peaks 5 to 10 years after treatment. The American Cancer Society reported that AML following treatment with topoisomerase inhibitors occurs within 2 to 3 years.[38] In addition, AML occurring in older ages may be coincidental and unrelated to any relevant occupational exposure that occurred in the distant past; yet these older AML cases could inflate the apparent latency.[39–42] Reasonable estimates for the maximum latency for acute leukemia associated with intense occupational exposure to benzene seem to be in the range of 5 to 10 or possibly 15 years.[26,27] Applying these latencies to the NCI industrial workers cohort, there is no clear evidence of an association with any exposure to formaldehyde, including peak exposure either as originally defined or as we redefined it.

Evaluation of other LHMs in the NCI cohort demonstrated no associations with cumulative or peak formaldehyde exposure metrics, consistent with other cohorts.

Reliance on mortality data for LHM may miss incident cases. This is especially true for HL for which the 5-year relative survival increased from 72% for the period 1979 to 1980 to approximately 88% for the period 2003 to 2009.[33] In contrast, the 5-year relative survival for AML increased from approximately 8% for the years 1978 to 1980 to approximately 25% during 2003 to 2009,[33] although 5-year relative survival is lower for individuals diagnosed at the age of 65 years and older.[33] Nevertheless, most AML deaths occurred more than 20 years after the last possible peak formaldehyde exposure, suggesting that marginally improved survival rates unlikely masked underlying true associations.

A further consideration for interpreting our findings is that biological mechanisms for the induction of leukemia by exogenous formaldehyde have not been established. Recent experimental studies have applied sensitive methods to distinguish endogenous formaldehyde concentrations in tissue from concentrations that result from exogenous formaldehyde exposure and have shown that formaldehyde present in protein adducts detected in the bone marrow derives exclusively from endogenous formation.[6,7] Formaldehyde does not form DNA:protein crosslinks[43,44] or DNA adducts[6] in bone marrow. The mounting mechanistic evidence is consistent with the body of epidemiological evidence—including these additional analyses of the NCI formaldehyde workers cohort—that occupational formaldehyde exposure does not increase risk of AML.

CONCLUSIONS

We replicated the associations of cumulative and peak formaldehyde exposures with HL previously reported from this cohort. Causal interpretations for the replicated associations with HL and the unanticipated association with CML are uncertain due to the absence of corroborative evidence from other epidemiologic studies of formaldehyde-exposed cohorts. Furthermore, the absence of established pathogenesis mechanisms for HL and CML raises doubt as to whether these observed associations are causal.

No other clear associations for peak or cumulative formaldehyde exposures were observed in this cohort for any of the specific LHM, including AML. Although our re-analysis using redefined "peak" exposure detected associations similar to those previously reported with the combined MLs, our new analyses of AML and CML mortality separately suggest that the observed patterns with

peak exposure were confined to CML. Furthermore, when taking into account the timing of peak exposure, no increased risk for AML is seen, as only one AML death occurred within 15 years of first, or even last, peak exposure. Sensitivity analyses assuming all the "unspecified" acute leukemia deaths were AMLs did not change these findings.

Our re-analysis of the data from the NCI cohort study of workers in the formaldehyde industries provides no support for the hypothesis that formaldehyde causes AML, the LHM of greatest prior concern.

ACKNOWLEDGMENTS

We obtained the NCI cohort data via a Data Transfer Agreement with the National Cancer Institute's Technology Transfer Center. We especially thank Laura Beane Freeman, PhD, and Patricia Stewart, PhD, of the National Cancer Institute (NCI) Division of Cancer Epidemiology and Genetics, and Laura A. Henmueller, PhD, of the NCI Technology Transfer Center. We also thank Haotian Wu for technical support in preparing the manuscript.

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