AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 56:1027–1039 (2013)

Cohort Mortality Study of Garment Industry Workers Exposed to Formaldehyde: Update and Internal Comparisons

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Background *To further evaluate the association between formaldehyde and leukemia, we extended follow-up through 2008 for a cohort mortality study of 11,043 US formaldehyde-exposed garment workers.*

Methods *We computed standardized mortality ratios and standardized rate ratios stratified by year of first exposure, exposure duration, and time since first exposure. Associations between exposure duration and rates of leukemia and myeloid leukemia were further examined using Poisson regression models.*

Results *Compared to the US population, myeloid leukemia mortality was elevated but overall leukemia mortality was not. In internal analyses, overall leukemia mortality increased with increasing exposure duration and this trend was statistically significant.*

Conclusions *We continue to see limited evidence of an association between formaldehyde and leukemia. However, the extended follow-up did not strengthen previously observed associations. In addition to continued epidemiologic research, we recommend further research to evaluate the biological plausibility of a causal relation between formaldehyde and leukemia.* Am. J. Ind. Med. 56:1027–1039, 2013. © 2013 Wiley Periodicals, Inc.

KEY WORDS: formaldehyde; cohort studies; occupational exposure; retrospective studies; leukemia

INTRODUCTION

Formaldehyde is ubiquitous in the environment, and in 1995 the Occupational Safety and Health Administration [1995] estimated that over two million US workers were occupationally exposed to formaldehyde. In 2009, an International Agency for Research on Cancer (IARC) Working Group reaffirmed that formaldehyde is carcinogenic in humans based on sufficient evidence in humans of nasopharyngeal cancer [Baan et al., 2009]. The Working Group also concluded that the evidence is sufficient for leukemia, particularly myeloid leukemia. In 2011, the National Toxicology Program reclassified formaldehyde as a known human carcinogen rather than a reasonably anticipated human carcinogen [National Toxicology Program, 2011]. Even so, the conclusion regarding leukemia is controversial because the mechanism by which formaldehyde could cause leukemia is unclear [Goldstein, 2011], although some have been proposed [Zhang et al., 2009; Viegas et al., 2010; Zhang, 2010].

In a recent meta-analysis of 14 studies of professional (e.g., embalmers, pathologists) and industrial workers, Schwilk et al. [2010] found that formaldehyde was associated with increased risks of leukemia mortality, especially myeloid leukemia mortality. Among three large

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Disclaimer: The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Disclosure Statement: The authors report no conflicts of interests.

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Accepted 27 March 2013

DOI 10.1002/ajim.22199. Published online 20 June 2013 in Wiley Online Library (wileyonlinelibrary.com).

occupational cohort mortality studies of formaldehyde-exposed industrial workers [Coggon et al., 2003; Pinkerton et al., 2004; Beane Freeman et al., 2009], the strongest epidemiologic evidence of an association of formaldehyde with leukemia and myeloid leukemia is based on results from the largest study (>25,000 workers), conducted by the National Cancer Institute (NCI) [Beane Freeman et al., 2009]. With follow-up through 1994, NCI investigators reported relative risks of 1.60 and 2.79 for leukemia and myeloid leukemia mortality, respectively, for the highest (≥4.0 ppm) versus lowest (>0 to <2.0 ppm) peak formaldehyde exposure category and a positive exposure–response relation between myeloid leukemia mortality and peak exposure. When follow-up was extended through 2004, the relative risk of myeloid leukemia mortality decreased but remained elevated. In contrast, Coggon et al. [2003] conducted a cohort mortality study of 14,014 British chemical workers and found no association between leukemia and formaldehyde exposure overall or among a subset of workers exposed to time weighted average levels above 2.0 ppm. Previously, we updated the third cohort mortality study, which involved >11,000 workers exposed to formaldehyde at any of three garment manufacturing facilities in Georgia and Pennsylvania [Pinkerton et al., 2004]. Based on mortality follow-up through 1998, we reported non-significant increases in multiple cause mortality from leukemia [standardized mortality ratio (SMR) 1.19, 95% confidence interval (CI) 0.81–1.68] and myeloid leukemia (SMR 1.38, 95% CI 0.80–2.20). The results for leukemia and myeloid leukemia as the underlying cause of death were similar (SMR 1.09 and 1.44, respectively). These results were driven by a 2.5-fold increase in multiple cause mortality from myeloid leukemia among workers with both 10+ years of exposure and 20+ years since first exposure (SMR 2.55, 95% CI 1.10–5.03) [Pinkerton et al., 2004].

In this study, to further evaluate the association between formaldehyde and leukemia we extended follow-up of the cohort of garment workers by 10 years. Leukemia, particularly myeloid leukemia, and nasopharyngeal cancers were the primary a priori outcomes for this study. Other a priori outcomes for which evidence of an association with formaldehyde exposure has been inconsistent included other lymphohematopoietic cancers [Beane Freeman et al., 2009; Hauptmann et al., 2009]; sino-nasal cancers [Barbieri et al., 2007; Blair et al., 1990; Bosetti et al., 2008; National Toxicology Program, 2010]; respiratory system, buccal cavity, and pharyngeal cancers [Blair et al., 1990; Laforest et al., 2000; Coggon et al., 2003; National Toxicology Program, 2010]; brain cancer [Walrath and Fraumeni, 1983; Blair et al., 1990; Band et al., 1997; Bosetti et al., 2008; Hauptmann et al., 2009]; and two non-malignant respiratory diseases [Coggon et al., 2003]—chronic obstructive pulmonary disease (COPD) and asthma [Bertazzi et al., 1989; Delfino et al., 2003; Rosenman, 2006; Bosetti et al., 2008; National Toxicology Program, 2010].

MATERIALS AND METHODS

Cohort

The cohort, assembled from personnel and union records, consists of 11,098 non-administrative employees who worked at any of three garment manufacturing facilities in Georgia (facilities 1 and 3) and Pennsylvania (facility 2) for at least 3 months after formaldehyde treated fabric was first introduced into the production process (1959 at facilities 1 and 2, 1955 at facility 3).

Formaldehyde Exposure

At these facilities, shirts were made from fabrics treated with formaldehyde resins to impart crease resistance and other desirable properties. Formaldehyde gas emitted from treated fabric during shirt production resulted in the potential for exposure. In the early 1980s, industrial hygiene monitoring for formaldehyde and potential confounding exposures (i.e., phenol, organic cleaning solvents, and nuisance dust) was conducted at each facility [Stayner et al., 1988]. Based on personal sampling among 549 employees (12–73 within each department), formaldehyde levels across all departments and facilities were similar with an overall geometric mean concentration of 0.15 ppm (geometric standard deviation = 1.90). Information on historical formaldehyde exposure levels was not available; however, due to reformulations of resins used to treat permanent press fabrics, formaldehyde levels were believed to have decreased over time. Duration of exposure (i.e., duration of employment after formaldehyde was introduced into the process) was used as a surrogate of exposure and estimated using general start and end dates from the records obtained from the facilities. In these facilities, the industrial hygiene surveys did not identify any other occupational chemical exposures likely to influence the study findings. Work history records were obtained from the facilities in the early 1980s. Work histories for workers actively employed at that time (n = 1,226) were truncated on the date the records were obtained (1981 for facilities 1 and 2, 1983 for facility 3); consequently, duration of exposure was underestimated for these workers (as in previous analyses of this cohort).

Ascertaining Vital Status

Vital status was ascertained through 2008. For the present update, follow-up included inquiry through the National Death Index (NDI), Social Security Administration (SSA), and the Internal Revenue Service. For deaths identified by NDI, causes of death were obtained from the NDI Plus service. For all other deaths, death certificates were

obtained from the state vital records offices and all causes of death listed were coded by trained nosologists according to the International Classification of Diseases revision in effect at the time of death.

Statistical Analysis

Cohort members with a missing date of birth (n = 55) were excluded from all analyses. Frequency distributions were calculated for sex, race (white, non-white), vital status (alive, dead, unknown), facility, year of first exposure, time since first exposure, and duration of exposure. Year of birth and age at first exposure were summarized using simple descriptive statistics. All descriptive analyses were conducted using SAS® version 9.2 (SAS Institute, Inc., Cary, NC).

Mortality was analyzed using a life-table analysis program, LTAS.NET [Steenland et al., 1998; Schubauer-Berigan et al., 2011]. Standard US population rate files created for LTAS.NET considered 92 (beginning in 1940) and 119 (beginning in 1960) cause of death categories based on the underlying cause of death [Robinson et al., 2006]. A second version of the 119 cause rate file considered all causes listed on the death certificate (i.e., multiple causes of death). For each cohort member, person-years at risk (PYAR) began to accumulate at the later of the rate file begin date or the completion date of the 3-month eligibility period. PYAR stopped accumulating at the earliest of the date of death for deceased cohort members, the study end date (December 31, 2008) for living cohort members, or the date last observed for persons lost to follow-up. The PYAR were stratified into 5-year intervals by age and calendar time and multiplied by the appropriate gender, race, and cause-specific mortality rates to calculate the expected number of deaths. For each outcome, the ratio of the observed to the total expected number of deaths was expressed as the SMR. Ninety-five percent CIs for the SMRs were calculated assuming that the number of observed deaths follows a Poisson distribution.

Additional underlying cause of death and multiple causes of death rate files were created specifically for nasopharyngeal and sino-nasal cancers (beginning in 1960) and subtypes of leukemia (beginning in 1968 when US mortality rates for acute and chronic leukemia subtypes first became available). To examine the possibility of geographic differences in mortality rates, all analyses were repeated using state-specific mortality rates, as appropriate by facility. All rate files were based on mortality statistics through 2007; consequently, mortality rates for 2005–2007 were used to calculate expected deaths for 2005–2008.

For a priori outcomes with more than 10 observed deaths, SMRs were stratified, using cut-points retained from the original study, by year of first exposure (<1963, 1963–1970, 1971+), duration of exposure (<3 years, 3–9 years, 10+ years), and time since first exposure (<10, 10–19, 20+ years). In addition, internal comparisons were made using directly standardized rate ratios (SRRs) for duration of exposure. SRRs were calculated using LTAS.NET as the ratio of standardized rates for the higher exposure categories compared to the lowest exposure category. Duration of exposure was lagged by 2 years for leukemia outcomes and 10 years for other lymphohematopoietic cancers, all solid cancers, and COPD. For leukemia, a 2-year lag period was selected to be consistent with the leukemia literature [Kubale et al., 2005, 2008; Richardson et al., 2008; Beane Freeman et al., 2009; Metz-Flamant et al., 2012] particularly the NCI study. Evaluation of different lag periods using a goodness of fit criterion is not informative in studies such as ours which used duration of exposure as the exposure metric since there is no within-person exposure variability over the exposure period [Richardson et al., 2011].

Relations between duration of exposure and rates of leukemia were further examined using Poisson regression modeling [Frome, 1983]. Cases of leukemia were identified using the underlying cause of death identified on the death certificate; additional modeling considered myeloid leukemia. Regression modeling was performed using the GENMOD procedure in SAS. To avoid bias associated with categorizing exposure and confounder data, regression modeling used ungrouped data [Loomis et al., 2005]. Effect modification was evaluated for year of first exposure (<1963, 1963–1970, and 1971+) using the likelihood ratio test for interaction. Potential confounders of the association between exposure and the rate of leukemia included age (centered at 70 years), year of birth (centered at 1920), gender, race, state (GA, PA), facility (1, 2, 3), year of first exposure (<1963, 1963–1970, and 1971+), and years since last exposure (<10, 10–19, 20+). Confounding was evaluated by comparing crude and adjusted exposure estimates and identified using a change-in-estimate criterion of 10%. Age and birth year were included as natural (restricted cubic) regression splines (with k = 3 knots at the 10th, 50th, and 90th percentiles of the case distribution) to minimize residual confounding [Hein et al., 2011].

In the Poisson regression models, duration of formaldehyde exposure was treated as a continuous variable and models were of the following general form:

$$\ln(\text{rate}) = \beta_0 + \beta_1 X_1 + \ldots + \beta_k X_k + \gamma f(E)$$

where X^1–X^k are covariates, E represents duration of exposure (years), f(E) is a function of exposure duration, and γ is the effect parameter. In addition to modeling exposure duration directly (untransformed, i.e., f(E) = E), we considered natural logarithm (i.e., f(E) = ln(E + 1)), and square root (i.e., $f(E) = E^{1/2}$) transformations; the interpretation of γ varied depending on the particular transformation [e.g., γ is the log rate ratio (RR) for a 1 year increase in exposure when exposure duration was untransformed].

CIs for parameter estimates were based on the profile likelihood. Models were informally compared using Akaike's Information Criterion (AIC) [Akaike, 1974]. Categorical (with five groups using cut-points selected to approximately evenly divide the leukemia cases) and natural (restricted cubic) spline (with k = 3 knots at the 10th, 50th, and 90th percentiles of the case exposure distribution) models were used to evaluate the continuous models. Two-sided $P < 0.05$ was considered statistically significant.

Several methods were used to account for potential latency in the regression models. First, a 2-year lag period was used to evaluate the different treatments of exposure (e.g., untransformed, log transformation). Next, age windows (exposure accrued prior to 35 years of age and exposure accrued at age 35 years or older), and time windows (exposure accrued 2 to <10, 10 to <20, and 20+ years prior) were evaluated. Several age window cut-points (25, 30, 35, 40, and 45 years) were evaluated and the 35-year cut-point produced the best fitting model (based on the model AIC). The cut-points of 2, 10, and 20 years for the time windows were selected to account for a 2-year lag period and as a comparison to Richardson [2008], who used cut-points of 10 and 20 years to evaluate the effects of benzene exposure on leukemia mortality.

To examine the effect of follow-up time on the RR, the best fitting model was re-evaluated for various follow-up years (1985–2008). Sensitivity analyses were conducted to estimate the impact of underestimating exposure duration for cohort members who were actively employed when the work histories were obtained. First, the work histories for 1,226 active workers were extended through the earliest of the date the worker would have been 65 years of age, the date last observed, or the plant closing date. Among workers who were already 65 years of age when the records were obtained (n = 12), half were assumed to have continued working 2 years and 8 months past age 65 (the mean duration of employment beyond age 65 years among "inactive" workers) and half did not have their work histories extended because they had already worked more than 2 years and 8 months past the age of 65. In a second scenario, the work histories for active workers were extended half way between when the records were obtained and the earliest of the date the worker would have been 65 years of age, the date last observed, and the plant closing date. Finally, results from Poisson regression models for leukemia based on the modified work histories were compared to results obtained with the truncated work histories.

Human Subjects' Protection

The study was approved by the NIOSH Human Subjects Review Board (protocol #08-DSHEFS-02xp/93-DSHEFS-02). Informed consent was waived for this records-based study because it involved minimal risk, did not adversely affect the rights and welfare of the subjects and could not practicably be carried out without the waiver.

RESULTS

The study included a total of 11,043 workers contributing 414,312 PYAR. Workers were predominantly white (76%) and female (82%; Table I). Causes of death were obtained for 3,904 (99.7%) of the 3,915 identified deaths. Forty-two percent of the cohort was first exposed before 1963, when formaldehyde levels were thought to be higher than in later years. The median duration of exposure

TABLE I. Characteristics of the Study Population

Characteristic	No.	%
Excluded from analysis[a]	55	<1
Number of workers	11,043	100
Race/sex		
White male	1,614	14.6
Non-white male	405	3.7
White female	6,738	61.0
Non-white female	2,286	20.7
Vital status (as of 12/31/2008)		
Alive	7,004	63.4
Dead[b]	3,915	35.5
Lost to follow-up	124	1.1
Facility		
1 (Georgia)	5,650	51.2
2 (Pennsylvania)	1,851	16.8
3 (Georgia)	3,542	32.1
Year of birth		
Median	1939	
Range	1882–1960	
Age at first exposure (years)		
Median	26	
Range	15−80	
Year of first exposure		
<1963	4,672	42.3
1963–1970	3,813	34.5
1971 or later	2,558	23.2
Time since first exposure		
<10 years	302	2.7
10–19 years	393	3.5
20+ years	10,348	93.7
Duration of exposure		
<3 years	5,294	47.9
3–9 years	3,140	28.4
10+ years	2,609	23.6

[a]Cohort members were excluded when date of birth was missing.
[b]Deaths from 1940 to 2008. There were 3,907 deaths from 1960 to 2008.

TABLE II. Standardized Mortality Ratios for All Causes, All Cancers, and Outcomes of A Priori Interest Among Garment Workers, 1960–2008*

Underlying cause of death (ICD-10 codes)	No. of deaths through 1998	No. of deaths through 2008	SMR (95% CI)
All causes	2,216	3,907	0.99 (0.96–1.02)
All cancers	611	1,021	0.96 (0.90–1.02)
Lymphohematopoietic cancers	59	107	1.11 (0.91–1.34)
Leukemia (C91.0–C91.3,C91.5–C91.9,C92–C95)	24	36	1.04 (0.73–1.44)
Myeloid leukemia (C92)	15	21	1.28 (0.79–1.96)
Acute myeloid leukemia (C92.0)[a]	9	14	1.22 (0.67–2.05)
Chronic myeloid leukemia (C92.1)[a]	4	5	1.35 (0.44–3.15)
Other and unspecified myeloid leukemia (C92.2–C92.9)	2	2	1.61 (0.20–5.82)
Lymphocytic leukemia (C91.0–C91.3,C91.5–C91.9)[b]	3	6	0.71 (0.26–1.56)
Other and unspecified leukemia (C93–C95)	6	9	0.92 (0.42–1.75)
Hodgkin disease (C81)	2	4	0.95 (0.26–2.44)
Non-Hodgkin lymphoma (C46.3,C82–C85,C88.0,C88.3,C91.4,C96)[b]	22	44	1.13 (0.82–1.52)
Multiple myeloma (C88.7,C88.9,C90)	11	23	1.24 (0.79–1.86)
Buccal cavity and pharyngeal cancers (C00–C14, C46.2)	8	13	0.89 (0.47–1.53)
Pharynx (C09–C14)	3	6	0.88 (0.32–1.92)
Nasopharynx (C11)[c]	0	0	0 (0–2.77)
Other/unspecified pharynx (C09–C10,C12–C14)	3	6	1.10 (0.40–2.39)
Other parts of buccal cavity (C03–C08,C46.2)	4	6	1.42 (0.52–3.09)
Lip or tongue (C00–C02)	1	1	0.28 (0.01–1.57)
Respiratory cancers (C30–C39)	153	273	1.03 (0.91–1.16)
Larynx (C32)	3	4	0.77 (0.21–1.97)
Trachea, bronchus, and lung (C33–C34)	148	267	1.04 (0.92–1.17)
Sino-nasal (C30–31)[c]	0	0	0 (0–3.89)
Other respiratory sites (C37,C38.0–38.3,C38.8,C39)	1	1	1.13 (0.03–6.28)
Brain cancer and other parts of nervous system (C47, C70–C72)	20	31	1.25 (0.85–1.78)
Selected non-malignant respiratory diseases			
Chronic obstructive pulmonary disease (J40–J44)	92	190	1.16 (1.00–1.34)
Asthma (J45–J46)	8	10	0.94 (0.45–1.72)

*ICD-10, International Classification of Diseases 10th revision; SMR, standardized mortality ratio (US referent rates); CI, confidence interval.
[a]Results for subtypes of myeloid leukemia begin in 1968, when US mortality rates for acute myeloid leukemia and chronic myeloid leukemia were first available.
[b]Chronic lymphocytic leukemia was classified as lymphocytic leukemia, consistent with previous analyses, instead of as non-Hodgkin lymphoma in accordance with current classification systems.
[c]Expected deaths for nasopharynx = 1.33, for sino-nasal = 0.95.

was 3.3 years and median time since first exposure was 39.4 years.

SMRs for all causes, all cancers, and outcomes of a priori interest based on US mortality rates are presented in Table II. Results for all cause of death categories are presented in Supplementary Table SI. Overall, mortality from all causes and all cancers was similar to that of the US population. Mortality was not statistically significantly elevated for any outcome of a priori interest. There were no deaths from nasopharyngeal (1.33 expected) or sino-nasal (0.95 expected) cancers. Results were generally very similar when analyses were repeated using US mortality rates for multiple causes of death or state-specific referent rates for underlying or multiple causes of death (Supplementary Table SII).

Associations With Year of First Exposure

Mortality for selected outcomes of a priori interest stratified by year of first exposure is presented in Table III. Compared to the US population, mortality from lymphohematopoietic cancers, leukemia, myeloid leukemia, acute myeloid leukemia, and non-Hodgkin lymphoma was highest among workers first exposed prior to 1963, when exposures to formaldehyde were presumably higher; however, none of these results were statistically significant. Lung cancer and multiple myeloma mortality was elevated among workers first exposed in 1971 or later, when formaldehyde levels were presumably lowest. For COPD, mortality was not elevated

TABLE III. Mortality From Selected Outcomes of A Priori Interest by Year of First Exposure and Time Since First Exposure Among Garment Workers, 1960–2008*

	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)	No. of deaths	SMR (95% CI)
	Year of first exposure					
Underlying cause of death	**Prior to 1963**		**1963–1970**		**1971 or later**	
Lymphohematopoietic cancers	77	1.20 (0.95–1.50)	22	0.93 (0.58–1.41)	8	0.93 (0.40–1.84)
Leukemia[a]	28	1.22 (0.81–1.77)	6	0.70 (0.26–1.53)	2	0.63 (0.08–2.28)
Myeloid leukemia	14	1.37 (0.75–2.30)	5	1.13 (0.37–2.63)	2	1.15 (0.14–4.17)
Acute myeloid leukemia[b]	11	1.55 (0.77–2.77)	2	0.64 (0.08–2.30)	1	0.83 (0.02–4.60)
Non-Hodgkin lymphoma[a]	32	1.19 (0.82–1.69)	10	1.11 (0.53–2.04)	2	0.65 (0.08–2.33)
Multiple myeloma	15	1.28 (0.71–2.11)	4	0.81 (0.22–2.08)	4	2.16 (0.59–5.52)
Trachea, bronchus, and lung cancer	149	0.93 (0.79–1.09)	83	1.15 (0.91–1.42)	35	1.47 (1.02–2.04)
Brain cancer and other parts of nervous system	18	1.16 (0.68–1.83)	10	1.48 (0.71–2.73)	3	1.25 (0.26–3.64)
Chronic obstructive pulmonary disease	124	1.03 (0.86–1.23)	50	1.46 (1.08–1.93)	16	1.74 (0.99–2.82)
	No. of deaths	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**	**No. of deaths**	**SMR (95% CI)**
	Time since first exposure					
Underlying cause of death	**<10 years**		**10–19 years**		**20+ years**	
Lymphohematopoietic cancers	4	0.61 (0.17–1.57)	10	0.84 (0.40–1.55)	93	1.19 (0.96–1.46)
Leukemia[a]	2	0.72 (0.09–2.61)	3	0.65 (0.13–1.89)	31	1.14 (0.77–1.62)
Myeloid leukemia	1	0.90 (0.02–4.99)	1	0.40 (0.01–2.21)	19	1.49 (0.90–2.32)
Acute myeloid leukemia[b]	0	0.00 (0.00–6.66)	0	0.00 (0.00–2.32)	14	1.50 (0.82–2.52)
Non-Hodgkin lymphoma[a]	1	0.52 (0.01–2.91)	3	0.70 (0.14–2.05)	40	1.22 (0.87–1.67)
Multiple myeloma	1	1.73 (0.04–9.61)	3	1.63 (0.34–4.76)	19	1.18 (0.71–1.84)
Trachea, bronchus, and lung cancer	12	1.57 (0.81–2.73)	25	0.97 (0.63–1.43)	230	1.03 (0.90–1.17)
Brain cancer and other parts of nervous system	2	0.87 (0.11–3.14)	4	0.97 (0.26–2.49)	25	1.37 (0.88–2.02)
Chronic obstructive pulmonary disease	1	0.46 (0.01–2.57)	11	1.28 (0.64–2.29)	178	1.16 (1.00–1.35)

*Outcomes of a priori interest with 10 or fewer observed deaths were excluded. *International Classification of Diseases* 10th revision codes for each cause are listed in Table II. SMR, standardized mortality ratio (US referent rates); CI, confidence interval.

[a]Chronic lymphocytic leukemia was classified as leukemia, consistent with previous analyses, instead of as non-Hodgkin lymphoma in accordance with current classification systems.

[b]Results for subtypes of myeloid leukemia begin in 1968, when US mortality rates for acute myeloid leukemia and chronic myeloid leukemia were first available.

among workers first exposed prior to 1963 whereas mortality was elevated among workers first exposed in 1963 or later.

Associations With Time Since First Exposure

SMRs for selected outcomes of a priori interest stratified by time since first exposure are presented in Table III. Compared to the US population, mortality was elevated for lymphohematopoietic cancers, particularly myeloid leukemia, brain cancer, and COPD among person-time with at least 20 years since first exposure; however, these results were not statistically significant. Compared to the US population, mortality was highest for multiple myeloma and lung cancer among person-time with <10 years since first exposure; however, the result for multiple myeloma was based on one observed death in this category.

Associations With Exposure Duration

SMRs and SRRs for selected outcomes of a priori interest stratified by duration of exposure (lagged by 2 years for leukemias and 10 years for other outcomes) are presented in Table IV. Among all leukemia outcomes there was a pattern of increased risk across increasing exposure duration categories. Overall, there was not a clear pattern of increased risk across exposure duration categories for any of the other a priori outcomes evaluated. Compared to the US population, the only statistically significant result observed for any lymphohematopoietic outcome was for multiple myeloma, for which a twofold increase in mortality was observed for the middle duration (3–9 years) category. For lung cancer, mortality was less than expected for the longest duration of exposure (10+ years) category compared to the US population. For COPD, mortality was elevated in the shortest

TABLE IV. Mortality From Selected Outcomes of A Priori Interest by Duration of Formaldehyde Exposure Among Garment Workers, 1960–2008*

Underlying cause of death Duration of exposure	No. of deaths	SMR (95% CI)	SRR (95% CI)
Lymphohematopoietic cancers[a]			
<3 years	37	0.97 (0.68–1.34)	1.00 (Referent)
3–9 years	32	1.18 (0.81–1.66)	1.05 (0.63–1.77)
10+ years	38	1.23 (0.87–1.69)	0.86 (0.52–1.41)
Leukemia[b,c]			
<3 years	8	0.65 (0.28–1.28)	1.00 (Referent)
3–9 years	9	0.88 (0.40–1.67)	1.14 (0.41–3.15)
10+ years	19	1.58 (0.95–2.47)	2.44 (0.94–6.30)
Myeloid leukemia[b]			
<3 years	4	0.65 (0.18–1.65)	1.00 (Referent)
3–9 years	7	1.46 (0.59–3.02)	2.12 (0.57–7.85)
10+ years	10	1.84 (0.88–3.38)	3.25 (0.84–12.63)
Acute myeloid leukemia[b,d]			
<3 years	2	0.46 (0.06–1.68)	1.00 (Referent)
3–9 years	5	1.52 (0.49–3.56)	4.71 (0.89–24.93)
10+ years	7	1.81 (0.73–3.73)	4.63 (0.92–23.19)
Non-Hodgkin lymphoma[a,c]			
<3 years	17	1.16 (0.68–1.86)	1.00 (Referent)
3–9 years	11	0.99 (0.49–1.77)	0.78 (0.35–1.76)
10+ years	16	1.21 (0.69–1.97)	0.71 (0.34–1.48)
Multiple myeloma[a]			
<3 years	8	1.16 (0.50–2.29)	1.00 (Referent)
3–9 years	11	2.03 (1.01–3.64)	1.22 (0.46–3.26)
10+ years	4	0.64 (0.17–1.64)	0.28 (0.08–0.99)
Trachea, bronchus, and lung cancer[a]			
<3 years	126	1.23 (1.02–1.46)	1.00 (Referent)
3–9 years	84	1.14 (0.91–1.42)	1.00 (0.75–1.33)
10+ years	57	0.71 (0.53–0.91)	0.74 (0.48–1.13)
Brain cancer and other parts of nervous system[a]			
<3 years	13	1.14 (0.60–1.94)	1.00 (Referent)
3–9 years	7	1.01 (0.41–2.09)	0.80 (0.30–2.17)
10+ years	11	1.72 (0.86–3.08)	1.21 (0.46–3.20)
Chronic obstructive pulmonary disease[a]			
<3 years	74	1.44 (1.13–1.80)	1.00 (Referent)
3–9 years	54	1.16 (0.87–1.51)	0.80 (0.55–1.18)
10+ years	62	0.94 (0.72–1.21)	0.66 (0.45–0.97)

*Outcomes of a priori interest with 10 or fewer observed deaths were excluded. *International Classification of Diseases* 10th revision codes for each cause are listed in Table II. SMR, standardized mortality ratio (US referent rates); SRR, standardized rate ratio; CI, confidence interval.

[a]Subject to a 10-year lag period.

[b]Subject to a 2-year lag period.

[c]Chronic lymphocytic leukemia was classified as leukemia, consistent with previous analyses, instead of as non-Hodgkin lymphoma in accordance with current classification systems.

[d]Results for subtypes of myeloid leukemia begin in 1968, when US mortality rates for acute myeloid leukemia were first available.

duration of exposure (<3 years) category compared to the US population. In internal analyses, standardized rates of multiple myeloma and COPD were significantly lower in the highest duration category than the lowest duration category.

Among person-time with 10+ years of exposure (unlagged) and 20+ years since first exposure, underlying cause mortality was elevated for leukemia (17 deaths, SMR 1.58, 95% CI 0.92–2.52) and myeloid leukemia (nine deaths, SMR 1.89, 95% CI 0.86–3.58), particularly

when multiple causes of death were considered (leukemia: 23 deaths, SMR 1.74, 95% CI 1.10–2.60; myeloid leukemia: 10 deaths SMR 1.90, 95% CI 0.91–3.50).

Poisson Regression Results for Leukemia

The effect of duration of exposure (lagged by 2 years) on leukemia and myeloid leukemia mortality rates was further evaluated using multivariable Poisson regression modeling adjusted for age, year of birth, and years since last exposure (Table V). For leukemia, year of first exposure did not modify the effect of exposure duration (interaction $P = 0.84$) and model fit was slightly better for the untransformed duration of exposure. For myeloid leukemia, the categorical model was best fitting. While all models for continuous treatments of exposure duration indicated a positive trend (Fig. 1A,B), only the continuous model for leukemia and the categorical model for myeloid leukemia were statistically significant. For both leukemia and myeloid leukemia, other than an elevation in the fourth category, the RRs did not increase with exposure duration category. We did not observe strong evidence of changes in the association between occupational formaldehyde exposure and leukemia mortality based on age at exposure or time since exposure windows (Table VI); however, adjusted rates of leukemia and myeloid leukemia were associated with recent exposure accrued at younger (<35 years) ages.

In the untransformed model for leukemia, when the follow-up year was extended by yearly increments (1985–2008), the 1-year RR ranged from 1.01 to 1.10 (Fig. 2A). CIs narrowed with additional follow-up, but only in the last 2 years did the adjusted RRs approach statistical significance. The overall pattern of risk for myeloid leukemia was similar to that for leukemia but the 1-year RR for myeloid leukemia ranged from 1.01 to 1.12, the CIs were wider and the RRs only approached statistical significance in 1991 and 1992 (Fig. 2B).

Sensitivity Analyses

Poisson regression results were similar in sensitivity analyses conducted to estimate the impact of underestimating

TABLE V. Poisson Regression Modeling for Leukemia (36 Cases) and Myeloid Leukemia (21 Cases) Among Garment Workers, 1960–2008

Outcome Model[a]	Exposure[b]	AIC[c]	Parameter estimate	Standard error	*P*-value[d]	Rate ratio (95% CI)[e]
Leukemia						
No transformation	$f(E) = E_{02}$	741.10	0.063	0.030	0.03 (1 df)	1.07 (1.01–1.13)
Log transformation	$f(E) = \ln(E_{02}+1)$	743.17	0.374	0.241	0.11 (1 df)	1.30 (0.95–1.83)
Square root transformation	$f(E) = E_{02}^{1/2}$	742.16	0.309	0.168	0.06 (1 df)	1.36 (0.99–1.91)
Categorical[f]	$E_{02} < 1.6$ years	742.58	0		0.06 (4 df)	1 (Reference)
	$1.6 \leq E_{02} < 6.5$ years		−0.142	0.543		0.87 (0.29–2.57)
	$6.5 \leq E_{02} < 16$ years		−0.043	0.553		0.96 (0.32–2.92)
	$16 \leq E_{02} < 19$ years		1.52	0.635		4.56 (1.30–16.2)
	$E_{02} \geq 19$		0.941	0.678		2.56 (0.68–9.91)
Myeloid leukemia						
No transformation	$f(E) = E_{02}$	467.65	0.040	0.038	0.30 (1 df)	1.04 (0.97–1.12)
Log transformation	$f(E) = \ln(E_{02}+1)$	467.94	0.268	0.306	0.37 (1 df)	1.20 (0.81–1.87)
Square root transformation	$f(E) = E_{02}^{1/2}$	467.77	0.207	0.214	0.33 (1 df)	1.23 (0.82–1.90)
Categorical	$E_{02} < 1.6$ years	462.30	0		0.01 (4 df)	1 (Reference)
	$1.6 \leq E_{02} < 6.5$ years		0.323	0.657		1.38 (0.39–5.51)
	$6.5 \leq E_{02} < 16$ years		−0.842	0.906		0.43 (0.06–2.39)
	$16 \leq E_{02} < 19$ years		1.86	0.788		6.42 (1.40–32.2)
	$E_{02} \geq 19$		0.538	0.940		1.71 (0.25–11.0)

[a]All models are adjusted for age (positive confounder) and year of birth (negative confounder) using restricted cubic spline terms and time since last employed (negative confounder) using three categories (active-<10 years (referent), 10 to <20 years, 20+ years).
[b]E_{02} represents exposure duration subject to a 2-year lag.
[c]AIC, Akaike's information criterion.
[d]*P*-value is based on the likelihood ratio test (df, degrees of freedom).
[e]With the exception of the categorical models, all rate ratios are for a 1-year increase in exposure duration. All 95% confidence intervals (CI) are based on the profile likelihood.
[f]Cut-points for the categorical model were selected to approximately evenly divide the leukemia cases. For the leukemia model, there are 7, 7, 8, 7, and 7 cases in each category, respectively; for the myeloid leukemia model, there are 4, 6, 2, 6, and 3 cases in each category, respectively.

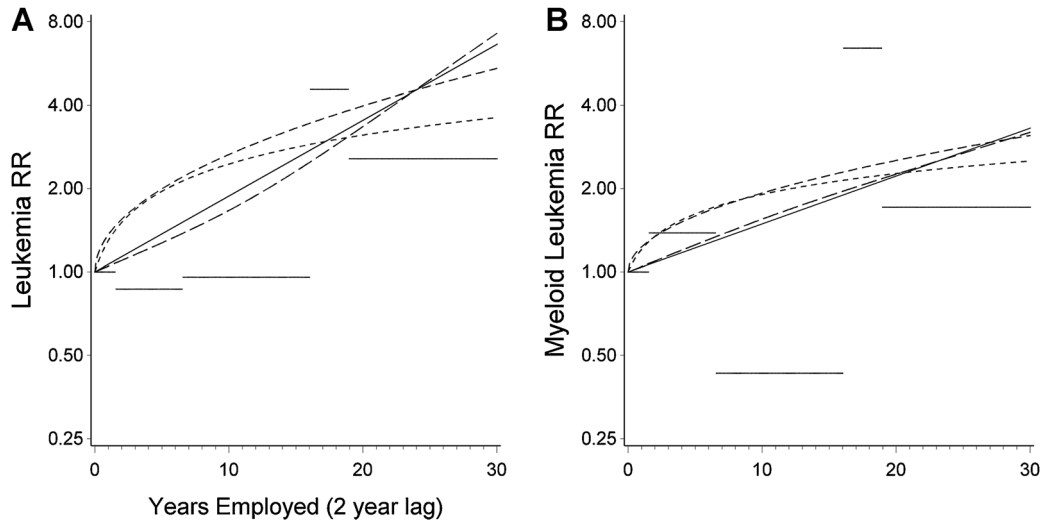

FIGURE 1. Age, birth year, and time since last exposure adjusted rate ratios (RRs) for all leukemia (**A**) and myeloid leukemia (**B**) with years of employment (i.e., exposure duration) lagged by 2 years. Solid curve represents the untransformed exposure duration, short dash the natural log transformation, medium dash the square root transformation, and long dash the restricted cubic spline model.

exposure for workers who were actively employed when the records were obtained. Under both scenarios, the exposure duration category (<1.6, 1.6 to <6.5, 6.5 to <16, 16 to <19, and 19+ years) was higher for approximately 6% of workers and remained unchanged for the remaining 94%.

DISCUSSION

Leukemia

We continue to see limited evidence of an association between formaldehyde exposure and leukemia mortality.

TABLE VI. Associations Between Leukemia (36 Cases) and Myeloid Leukemia (21 Cases) Mortality and Years of Exposure to Formaldehyde From Poisson Regression Models Among Garment Workers, 1960–2008

	Rate ratio at 1 year of exposure (95% confidence interval)[a]								
Outcome / **Cumulative exposure**	**Model[b]**	**AIC[c]**	***P*-value[d]**	**Accrued at any age**	**Model**	**AIC**	***P*-value**	**Accrued at <35 years of age[e]**	**Accrued at ≥35 years of age**
Leukemia									
≥2 years prior	1	741.10	0.03 (1 df)	1.07 (1.01–1.13)	2	741.78	0.05 (2 df)	1.14 (1.00–1.28)	1.05 (0.98–1.12)
2 to <10 years prior	3	743.59	0.10 (3 df)	0.92 (0.72–1.17)	4	742.60	0.04 (6 df)	1.54 (0.94–2.36)	0.86 (0.64–1.11)
10 to <20 years prior				1.09 (0.94–1.29)				1.32 (0.88–1.78)	1.07 (0.91–1.27)
≥20 years prior				1.07 (1.01–1.14)				1.09 (0.93–1.24)	1.06 (0.99–1.14)
Myeloid leukemia									
≥2 years prior	1	467.65	0.30 (1 df)	1.04 (0.97–1.12)	2	468.89	0.40 (2 df)	1.10 (0.94–1.27)	1.02 (0.94–1.11)
2 to <10 years prior	3	470.21	0.47 (3 df)	0.93 (0.68–1.25)	4	468.07	0.10 (6 df)	1.70 (0.98–2.93)	0.84 (0.57–1.18)
10 to <20 years prior				1.15 (0.94–1.45)				1.40 (0.91–2.00)	1.12 (0.90–1.45)
≥20 years prior				1.03 (0.95–1.12)				1.01 (0.81–1.21)	1.03 (0.94–1.14)

[a]Rate ratios are adjusted for age (positive confounder) and year of birth (negative confounder) using restricted cubic spline terms and time since last employed (negative confounder) using three categories (active-<10 years (referent), 10 to <20 years, 20+ years); 95% confidence intervals are based on the profile likelihood.
[b]All models exclude exposures accrued <2 years prior (i.e., lagged by 2 years). Model 1 considers cumulative exposure (lagged by 2 years); model 2 classifies cumulative exposure according to age at exposure windows; model 3 classifies cumulative exposure according to exposure time windows; and model 4 considers a cross-classification of age at exposure and time since exposure windows.
[c]AIC, Akaike's information criterion.
[d]*P*-value is based on the likelihood ratio test (df, degrees of freedom).
[e]The age cut-point of 35 years minimized the model AIC among all cut-points evaluated (25, 30, 35, 40, and 45 years).

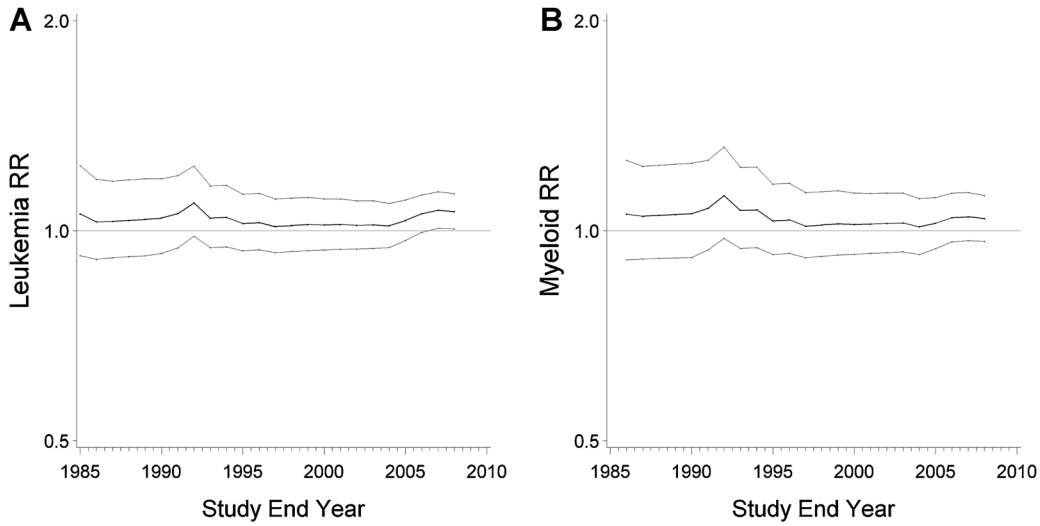

FIGURE 2. Results of Poisson regression modeling by study end year for leukemia (**A**) and myeloid leukemia (**B**). Rate ratios (RR) and 95% confidence bounds for a 1-year increase in exposure duration (lagged by 2 years) were adjusted for age, year of birth, and time since last exposure.

Although leukemia mortality was similar to that of the US population in the overall cohort, it was elevated among workers with both 10+ years exposure duration and 20+ years of potential latency, especially when all causes listed on the death certificate were considered. Also consistent with a causal association, compared to the US population, leukemia mortality was highest among workers first exposed prior to 1963 when exposure levels were presumably higher. In internal analyses, a statistically significant positive trend was observed for leukemia with 2-year lagged exposure duration. Our findings that indicate an association between formaldehyde exposure and elevated leukemia mortality are consistent with a recent meta-analysis for leukemia [Schwilk et al., 2010] and with the NCI study, which found an association between peak ($\geq$2.0 ppm) formaldehyde exposure compared to the referent category ($>$0 to $<$2.0 ppm) and increases in myeloid leukemia mortality with follow-up through early 1990s [Beane Freeman et al., 2009]. In the NCI study, analyses of peak formaldehyde exposure for varying follow-up end years (1965–2004) consistently observed higher relative risks in the medium peak (2.0 to $<$4.0 ppm) and high peak ($\geq$4.0 ppm) exposure categories relative to the low peak ($>$0 to $<$2.0 ppm) exposure category for myeloid leukemia compared to leukemia. The NCI peak exposure category was based on the maximum peak. For jobs without peak exposures that exceeded the time weighted average exposure category assigned in the study, the peak exposure category was equivalent to the time weighted average category. In contrast, in the large British cohort of formaldehyde-exposed chemical workers, leukemia mortality was not elevated overall nor was it elevated among a subset of highly exposed (time weighted average $>$2.0 ppm) workers [Coggon et al., 2003].

In the 1980s, formaldehyde levels were similar across the three facilities and departments included in our study and the geometric mean concentration of 0.15 ppm was comparable to the low exposure groups considered by Bean Freeman et al. (peak: 0 to $<$2.0 ppm, time weighted average: $>$0 to $<$0.5) and Coggon et al. (time weighted average: 0.1–0.5 ppm). Based on historical measurements in the garment industry, however, formaldehyde levels at these facilities in earlier years may have been more similar to formaldehyde exposures experienced by the NCI and British cohorts. According to Goldstein [1973], the textile industry made a concerted effort in the late 1960s and early 1970s to reduce the amount of formaldehyde used to treat fabric as evidenced by measured formaldehyde levels in cutting rooms decreasing from 10 ppm in 1968 to 2 ppm in 1973. Furthermore, average levels of formaldehyde in the garment industry were characterized as 0.3–2.7 ppm among eight US garment plants in 1966 and industry average levels in the 1970s and 1980s were characterized as 0.2–2 ppm [International Agency for Research on Cancer, 2006].

Compared to the previous update, our point estimates for the overall cohort and for high exposure subgroups (based on year of first exposure or exposure duration) were consistently lower for myeloid leukemia and about the same for leukemia. Diminishing risk with extended follow-up has been observed for known leukemogens [Silver et al., 2002] and was observed in the NCI cohort [Beane Freeman et al., 2009]. When we evaluated the effect of follow-up time on the risk of leukemia, RRs remained near unity for all time periods. For

myeloid leukemia we observed an overall decline in risk towards unity through 1997. The RR for myeloid leukemia approached significance only in 1992. When we examined time windows, we observed little evidence of increased leukemia or myeloid leukemia risk with more recent exposure in the overall cohort. However, unexpectedly, the risk of leukemia and myeloid leukemia mortality was higher with recent exposure accrued at younger ages (<35 years). Richardson [2008] observed that leukemia mortality was associated with more recent (within 10 years) benzene exposure accrued at older (>45 years) ages in a cohort of 1,845 rubber hydrochloride workers. Richardson hypothesized that benzene affects the later stages of leukemia pathogenesis. Unless our finding occurred due to chance, our results may suggest that the role of formaldehyde in the pathogenesis of leukemia is different than benzene.

Other Lymphohematopoietic Cancers

Mortality from lymphohematopoietic cancers was slightly, but not significantly, elevated. In comparison, in the NCI cohort, mortality from lymphohematopoietic cancers was not elevated compared to that of the US population but was associated with high peak (≥4.0 ppm) exposure [Beane Freeman et al., 2009] when compared to the referent category (0 to <2.0 ppm). In our study, mortality from multiple myeloma and non-Hodgkin lymphoma contributed to the slight excess in lymphohematopoietic cancer mortality. Multiple myeloma mortality was highest among workers first exposed after 1970 when exposure levels were presumably lower and for workers in the middle exposure duration category and with <10 years since first exposure. These findings suggest that the increase in multiple myeloma mortality is not due to formaldehyde exposure. In contrast, multiple myeloma risk was significantly elevated in a meta-analysis of nine studies of formaldehyde-exposed workers [Zhang et al., 2009]. Our findings for non-Hodgkin lymphoma were equivocal. Non-Hodgkin lymphoma mortality was highest for person-time with 20+ years since first exposure and for workers first employed prior to 1971, but did not increase across exposure duration categories. Non-Hodgkin lymphoma mortality was not associated with formaldehyde exposure in the NCI study [Beane Freeman et al., 2009], the British study of formaldehyde-exposed chemical workers [Coggon et al., 2003], or a meta-analysis of 11 studies [Zhang et al., 2009]. No occupational studies of formaldehyde-exposed workers have observed a statistically significant increase in risk for non-Hodgkin lymphoma [National Toxicology Program, 2010]. In contrast to the NCI study, which observed elevated mortality from Hodgkin disease and significant associations with peak (≥2.0 ppm) and average (≥0.5 ppm) formaldehyde exposure compared to referent groups [Beane Freeman et al., 2009], we did not observe an increase in Hodgkin disease mortality (four deaths). No increase in risk of Hodgkin disease mortality has been associated with formaldehyde exposure in other studies [National Toxicology Program, 2010].

Other A Priori Outcomes

With regard to non-lymphohematopoietic outcomes, SMRs for a priori outcomes were similar to results from the previous update (through 1998). Specifically, as in the prior update, there was little evidence for an increased risk of mortality from buccal cavity cancers, pharyngeal cancers (including nasopharynx), or respiratory cancers. Although lung cancer mortality was elevated in some sub-groups, lung cancer mortality was highest for those who were first exposed after 1970, when formaldehyde levels were thought to be lowest, and among those with the shortest duration of exposure. In the NCI study, formaldehyde exposure was not associated with lung cancer [Hauptmann et al., 2004]. In the British cohort study of formaldehyde-exposed chemical workers, lung cancer mortality was significantly elevated overall and highest among men who had worked in jobs with the highest (time weighted average >2 ppm) levels of exposure when compared to national lung cancer rates; however, lung cancer mortality was not associated with years of employment in high exposure jobs [Coggon et al., 2003]. A 1997 meta-analysis of 24 epidemiologic studies reported no association between formaldehyde exposure and lung cancer [Collins et al., 1997].

Evidence of an association of brain cancer mortality with formaldehyde exposure was also not compelling in this cohort study which is consistent with results among other industrial cohorts [National Toxicology Program, 2010]. In contrast, an increase in brain cancer mortality has been observed among professional workers in cohort studies [Bosetti et al., 2008]. However, in a nested case–control study of embalmers and funeral directors [Hauptmann et al., 2009] investigators did not find a statistically significant association between brain cancer and ever-embalming or several quantitative measures of formaldehyde exposure (cumulative, peak, or average exposure).

Although COPD mortality among our cohort was elevated, results of our stratified analyses did not provide evidence of a causal association between formaldehyde exposure and COPD. For example, COPD mortality was lowest among workers hired prior to 1963, when formaldehyde levels were thought to be highest. Similarly, COPD mortality was highest among workers exposed to formaldehyde for <3 years. Existing epidemiologic data on COPD mortality and formaldehyde exposure are limited. Among a cohort of British chemical workers, Coggon et al. observed an increased risk of respiratory disease mortality overall; over half of the respiratory disease deaths were from COPD [Coggon et al., 2003]. Across the exposure categories, a statistically significant positive exposure–response trend was observed among the overall cohort compared to the national

population; however, there was not a positive exposure–response trend across five exposure categories when compared to the local population for the overall cohort or for workers employed at the factory where 92% of the highest level (>2.0 ppm) exposure occurred.

Strengths and Limitations

Strengths of the current study include the large cohort size, extended follow-up period, inclusion of many female participants, use of internal comparisons, and absence of potential confounding exposures in the facilities. Some limitations of this study include the lack of quantitative formaldehyde exposure estimates; the relatively low level of formaldehyde exposure measured at the facilities in the early 1980s; the lack of quantitative data on exposure levels in prior years; the lack of data on smoking; the reliance on mortality data; and limited power to assess mortality for rare outcomes such as nasopharyngeal, sino-nasal cancers, and some of the secondary a priori causes of death. Due to a lack of quantitative formaldehyde exposure data it was not possible to assess cumulative or peak exposure, as in the NCI study. Furthermore, incidence studies are preferred over mortality studies for cancers with relatively high survival rates, such as lymphohematopoietic cancers [Linet and Devesa, 2002; International Agency for Research on Cancer (IARC)/National Occupational Research Agenda expert group, 2010]. In the United States, the overall 5-year relative survival rate for leukemia ranged from 34.4% to 56.6% between 1975 and 2007 [Howlader et al., 2010]. Incidence based cancer morbidity research may be helpful in clarifying the association between formaldehyde exposure and leukemia outcomes. Another potential limitation is possible underascertainment of myeloid leukemia. Overall, the accuracy of death certificates where leukemia is the underlying cause is high, but myeloid leukemia in particular is often misclassified as "other and unspecified" leukemia [Percy et al., 1990]. Also, we underestimated exposure (employment) for some workers because we assumed that exposure stopped in the early 1980s, when records were obtained; however, in sensitivity analyses we observed that the effect of underestimating exposure for these workers was likely to be minimal.

CONCLUSIONS

In conclusion, we continue to see limited evidence of an association between formaldehyde and leukemia. However, the extended follow-up did not strengthen previously observed associations. Compared to another larger, industrial US cohort study that had quantitative measures of exposure, the leukemia findings in our study are less convincing. In addition to continued epidemiologic research we recommend further research to evaluate the biological plausibility of a causal relation between formaldehyde and leukemia. We did not find solid evidence of increased mortality from other lymphohematopoietic cancers, a priori solid cancers, COPD or asthma associated with formaldehyde exposure.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Supplementary Table SI. Standardized Mortality Ratios for Garment Workers, 1940–2008

Supplementary Table SII. Standardized Mortality Ratios for Causes of Death of A Priori Interest Among Garment Workers by Referent Rate File, 1960–2008