Formaldehyde and Leukemia: An Updated Meta-Analysis and Evaluation of Bias

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Objective: Formaldehyde exposures are common, and data linking these exposures to leukemia have been mixed and controversial. The objective of this analysis is to review the current epidemiologic literature on formaldehyde and leukemia. **Methods:** We performed an updated meta-analysis focusing on high-exposure groups and myeloid leukemia and included two large recent studies: one involving >25,000 workers in US formaldehyde industries and the other involving a cohort of >13,000 funeral directors and embalmers. **Results:** Formaldehyde was associated with increased risks of leukemia (relative risk = 1.53; 95% confidence interval = 1.11 to 2.21; P = 0.005; 14 studies), specifically myeloid leukemia (relative risk = 2.47; 95% confidence interval = 1.42 to 4.27; P = 0.001; 4 studies). **Conclusion:** These findings provide evidence of increased myeloid leukemia risk with exposure to formaldehyde.

Millions of people in the United States and worldwide are exposed to formaldehyde in the workplace,[1] and environmental exposures may be even more common. In a recent study, 38% of Federal Emergency Management Agency supplied trailers used after Hurricane Katrina had formaldehyde levels >0.1 ppm,[2] a level over six times higher than the recommended exposure limit of 0.016 ppm.[3]

The International Agency for Research on Cancer has classified formaldehyde as a group 1 human carcinogen based on sufficient evidence in humans that formaldehyde causes both nasopharyngeal cancer and leukemia.[4] Nevertheless, these conclusions have been controversial. For example, some authors have noted that the human epidemiologic evidence on nasopharyngeal cancer is heavily reliant on a cluster of cases from a single US factory.[5,6] And, although a recent meta-analysis by our research group found evidence of an association between formaldehyde and leukemia,[7] other meta-analyses have not reported clear associations.[5,6,8]

There may be several reasons for these discrepant results for leukemia. One is that, in some studies, all subtypes of leukemia are combined, despite the possibility that not all subtypes may be related to formaldehyde. The second reason is that, in some studies, all cohort members were combined into a single "exposed" group, despite the fact that some cohort members (eg, administrative or management staff) may have had very low or no formaldehyde exposure. The third issue is the healthy worker effect.[9] This may occur in studies that compare workers with the general population, which contains many people who cannot work because of health conditions including cancer. If true associations exist, failure to account for each of these three factors could drive relative risk (RR) estimates toward 1.0 and could limit the ability of studies and meta-analyses to identify real effects.

This article presents an updated meta-analysis on formaldehyde and leukemia, which includes two large recently published studies not used in our previous meta-analyses. The first new study is a case-control investigation nested in a large cohort of >13,000 US funeral directors and embalmers, occupations with known high formaldehyde exposure.[10] The second is the National Cancer Institute's formaldehyde cohort study that involves >40 years of follow-up and includes >25,000 workers from 10 US formaldehyde-producing or formaldehyde-using plants.[11] Because of their large sizes, these new studies add substantially to the precision with which formaldehyde-leukemia associations can be assessed.

The major goals of this meta-analysis are to summarize the current epidemiologic literature and to explore the impacts of various factors that may affect the interpretation of these data. Several issues are evaluated including 1) the impact of combining workers with high and low exposure; 2) the effect of including subtypes of leukemia that may not be associated with formaldehyde; 3) the potential role of the healthy worker effect; and 4) the possible differences between industry workers and professional workers such as funeral directors and embalmers. This is the first meta-analysis to objectively explore all of these issues and the first to include both of the new large studies mentioned above. Other major tenets of causal inference are also assessed including biologic plausibility, the possibility that elevated RRs in professionals may be because of confounding, and an evaluation of possible dose-response relationships.

METHODS

Multiple sources including PubMed were searched for all epidemiologic studies on leukemia and formaldehyde exposure or formaldehyde-using industries and occupations. Searches included the keywords formaldehyde, leukemia, lymphohematopoietic, cancer, myeloid, and others. Bibliographies of all articles included in the meta-analysis, all relevant review articles, and previous meta-analyses were also searched. Only data published in peer reviewed scientific journals or edited books were used in our primary analyses. Government reports were excluded but evaluated in sensitivity analyses in which these studies are included.[12,13] Other studies were excluded for the following reasons: 1) RRs or estimates of variance were not provided or could not be estimated[14,15]; 2) study subjects were the same as those used in an another included study[16–21]; 3) there was no clear formaldehyde-exposed group[22,23]; 4) RRs were reported only as standardized proportionate cancer incidence ratios, which can be biased if formaldehyde or a correlated exposure (eg, asbestos and silica) increases the risks of other cancer types.[24] Sensitivity analyses were done to evaluate the impact of these exclusions.

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Searches included both case-control and cohort studies, although only three case-control studies met our initial inclusion criteria.[10,25,26] The case-control study by Hauptmann et al[10] was included in the meta-analysis because it was nested in a large cohort of US embalmers. Another nested case-control study, Partanen et al,[26] was excluded because exposure was assessed much differently in cases (personal interviews and company records) than in controls (only company records). This left only the population-based case-control study by Blair et al,[25] which had only one myeloid leukemia case in the high-exposure group. This study was excluded from our main analyses because significant formaldehyde exposure is much less likely in population-based studies than in studies that take place in cohorts of highly exposed workers. Nevertheless, a sensitivity analysis was done to assess the impact of this exclusion.

Several publications reported results on the same cohort. In these instances, only the most recent publication was included, unless 1) only the less recent publication reported data specifically on myeloid leukemia or 2) only the less recent study reported data for a highly exposed group (defined later). We focused on myeloid leukemia because previous evidence suggests that associations with formaldehyde may be strongest for this subtype.[7] If data were given for myeloid leukemia, those data were used. Otherwise, RRs for all leukemia subtypes combined were used in the main analysis. If formaldehyde is associated with a particular subtype of leukemia (eg, myeloid), but not other subtypes, combining all subtypes together could bias summary RRs toward the null. Because of this, a separate analysis was done that only included data on myeloid leukemia. And, to evaluate the magnitude of the potential bias caused by including unrelated leukemia subtypes, the myeloid-only analysis was compared with a separate analysis that included only RRs in which all leukemia subtypes were combined.

The major goal of this meta-analysis was to evaluate whether formaldehyde is associated with leukemia and not to define exact dose-response relationships or to evaluate risks in people with low exposures. The simple type of cause and effect relationship we sought to evaluate is best assessed in groups with high exposures. This is because, if a true relationship exists, RRs are likely to be higher in groups with high exposure than in groups with low exposure. All else being equal, higher RRs have greater statistical power than lower RRs (ie, those just >1.0). In addition, higher RRs are less likely to be solely because of confounding or other bias.[27–29] Because of these factors, when studies provided RR estimates for different levels of exposure (eg, low, medium, and high), the RR for the highest level was used in the main meta-analysis. Nevertheless, in addition, a separate analysis was also done in which we evaluated each study for evidence of dose-response relationships.

Several studies did not specifically report data on highly exposed workers but only provided RRs for their entire cohort as a whole. Nevertheless, several of these cohorts included workers with high exposure (eg, >0.75 ppm, the permissible exposure limit [PEL]) and workers with low or no exposure. If a true association exists, including workers with very low or no exposure in the exposed group can dilute RR estimates toward 1.0. To evaluate this issue, we performed a subgroup meta-analysis that only included studies reporting RRs in highly exposed groups. For this analysis, high exposure was defined as an average or peak exposure above the PEL (0.75 ppm) or short-term exposure limit (STEL; 2 ppm), respectively; an exposure duration of $\geq$10 years; or work in a formaldehyde-producing facility before 1961. For comparison, we also performed an analysis that only included studies in which the exposed group included all cohort members, regardless of whether their exposures were high, low, or none.

In many of the studies included in this meta-analysis, different types of exposure metrics were used. For example, Hauptmann et al[10] reported separate RRs for peak exposure, average intensity, cumulative exposure, and duration. Other studies only gave data for one metric. In observational epidemiology, it is uncommon for all, or even most, studies on a given topic to report data using the exact same exposure metric. As a consequence, meta-analyses of epidemiologic data frequently combine RRs based on different metrics and different exposure categorizations. Our meta-analysis is no different. When RRs for different exposure metrics were given, we selected one in the following order: peak exposure, average intensity, cumulative exposure, exposure duration, and earlier date of hire. Peak exposure was chosen first *a priori* because metrics such as average intensity and cumulative exposure may be less accurate measures of true exposure if workers with very high exposure also have long intervening periods with little or no exposure.[30,31]

Microsoft Excel 2008 for Mac version 12.2.3 and STATA version 8.0 (College Station, TX) were used for all calculations. Summary RR estimates were calculated using both the fixed effects inverse variance weighting method[32] and the random effects method.[33] Heterogeneity was evaluated using the general variance-based method.[34] If heterogeneity is present, the random effects model incorporates between-study variation into the summary variance estimate and confidence intervals (CI)s. Some authors have suggested that the random effects model may be more conservative.[34] Nevertheless, unlike the fixed effects model, where weights are directly proportional to study precision, the random effects model weights studies are based on a highly complex and nonintuitive mix of study precision, RR, and meta-analysis size (ie, the number of studies included).[33] As a consequence, this model assigns greater weight to smaller studies than the fixed effects model and, therefore, may actually be less conservative.[35] To avoid this problem, we used the method presented by Shore et al[36] and used in several subsequent meta-analyses.[37–41] In this method, the summary RR estimate is calculated by directly weighing individual studies by their precision, whereas between-study heterogeneity is only incorporated into the summary RR's variance (ie, the 95% CI).

Occupational studies reporting standardized mortality ratios (SMRs) can be biased by the healthy worker effect.[9] To objectively evaluate the impact of this, separate analyses were performed, in which SMRs were adjusted for this potential bias using the SMRs for all-cause mortality (or all-cancer mortality when all-cause data were not available) and the methods described by Miettinen and Wang[42] and Smith et al.[43] All-cancer mortality was not selected first because formaldehyde or some other possibly correlated exposure (eg, silica and asbestos) may increase the risks of some cancers and mask an otherwise true healthy worker effect.

In Hauptmann et al,[10] RRs were provided using two different comparison groups: those who conducted <500 embalmings and those who conducted no embalmings.[10] The former was chosen because the later included very few subjects and led to unstable RR estimates. This resulted in a more conservative estimate because the RR using the latter group was higher (RR = 2.9 vs 13.0). Funnel plots and Egger's and Begg's tests were used to evaluate publication bias.[44,45] Missing CIs in cohort studies were calculated using Byar's approximation.[46] All P values are one-sided (unless otherwise reported) given our clear *a priori* hypothesis that formaldehyde increases, not decreases, leukemia risk.

RESULTS

Table 1 shows the results and weights of the studies used in this meta-analysis. In total, 13 cohort studies and 1 nested case-control study were included. Six studies were from professional groups, and eight studies were from industry groups. No study received $>20\%$ of the weight in the fixed effects model.

Table 2 summarizes the results of the meta-analysis. The summary RR for all studies combined was 1.53 (95% CI = 1.11 to 2.11; $P = 0.005$; Fig. 1). Summary RRs in industry workers and

TABLE 1. Description of Studies in the Current Meta-Analysis

Author	RR	95% CI	%W	Type	*N*	Location	Outcome (ICD)	Exposure Category
Andjelkovich et al[51]	0.43	0.05–1.57	2.2	Coh/SMR	2	Iron foundry	Leukemia 204–7	Exposed
Beane Freeman et al[11]	1.78	0.87–3.64	12.8	Coh/RR	19	10 US formaldehyde industries	Myeloid 205	Peak 4+ ppm
Coggon et al[49]	0.71	0.31–1.39	11.7	Coh/SMR	8	6 United Kingdom chemical plants	Leukemia 204–8	Average 2+ ppm
Dell and Teta[47]	2.65	1.15–5.24	11.4	Coh/SMR	8	Plastics manufacturing	Leukemia	R and D workers
Hall et al[69]	1.52	0.41–3.89	5.2	Coh/SMR	4	United Kingdom pathologists (1974–1987)	Leukemia	Total cohort
Harrington and Shannon[50]	0.63	0.01–3.48	0.8	Coh/SMR	1	United Kingdom pathologists/laboratory technicians (1955–1973)	Leukemia 204–7	Pathologists
Harrington and Shannon[50]	0.45	0.01–2.53	0.9	Coh/SMR	1	United Kingdom pathologists/laboratory technicians (1955–1973)	Leukemia 204–7	Laboratory technicians
Hauptmann et al[10]	2.90	0.90–9.50	4.7	NCC	11	US embalmers and funeral directors	Myeloid 205	Peak 9.3+ ppm
Levine et al[70]	1.60	0.43–4.10	5.2	Coh/SMR	4	Ontario undertakers	Leukemia 204–7	Total cohort
Pinkerton et al[71]	2.19	0.94–4.32	11.3	Coh/SMR	8	US garment facilities	Myeloid 205	Duration 10+ yr
Stellman et al[52]	0.96	0.54–1.71	19.7	Coh/RR	12	ACS US population cohort	Leukemia	Exposed
Stern et al[72]	1.70	0.63–3.73	8.3	Coh/SMR	6	Tannery workers	Leukemia 204	Duration 10+ yr
Stroup et al[48]	8.80	1.80–25.50	3.7	Coh/SMR	3	US anatomists	Myeloid*	Total cohort
Wong[73]	1.35	0.15–4.87	2.2	Coh/SMR	2	Formaldehyde chemical plant	Leukemia 204–7	Employed before 1961

*Chronic myeloid leukemia only (data not given for acute myeloid leukemia) for year in which specific reference subtype data were available (1969–1979).

ACS, American Cancer Society Cancer Prevention Study II; Coh, cohort study; *N*, number of exposed cases; NCC, nested case-control study; R and D, research and development; %W, percent weight given in the fixed effects model.

TABLE 2. Results of Meta-Analysis of Formaldehyde and Leukemia

			Fixed Effects		Shore-Adjusted 95% CI	Random Effects		Heterogeneity	
	Studies	Cases*	RR	95% CI		RR	95% CI	χ^2	*P*
All studies	14	89	1.53	1.18–1.98	1.11–2.11	1.58	1.12–2.24	20.66	0.08
Leukemia type									
Myeloid only	4	41	2.47	1.57–3.86	1.42–4.27	2.64	1.49–4.69	4.50	0.21
All leukemias combined†	16	193	1.42	1.21–1.67	—	—	—	11.42	0.72
High exposure vs all exposed									
High exposure	6	54	1.55	1.08–2.22	1.04–2.31	1.57	1.04–2.36	6.24	0.28
All exposed‡	16	185	1.07	0.90–1.26	0.86–1.32	1.16	0.90–1.51	24.93	0.05
Healthy worker effect adjusted									
All studies	14	89	1.72	1.34–2.21	1.18–2.51	1.86	1.23–2.82	29.67	0.01
Myeloid only	4	41	2.77	1.79–4.30	1.39–5.52	3.21	1.55–6.67	7.41	0.06
Sensitivity analyses									
Exclude Dell and Teta[47]	13	81	1.42	1.08–1.87	1.02–1.99	1.49	1.03–2.14	18.38	0.10
Add excluded studies§	18	124	1.45	1.18–1.78	1.15–1.83	1.41	1.08–1.84	21.87	0.19
Add Blair et al[25]	15	90	1.51	1.17–1.95	1.10–2.06	1.56	1.11–2.19	21.26	0.10
Professional workers	6	24	2.27	1.29–3.99	1.15–4.45	2.21	1.09–4.49	7.08	0.21
Industry workers	8	65	1.38	1.04–1.84	0.96–1.99	1.39	0.95–2.04	11.25	0.13
Industry: high exposure	5	43	1.45	1.00–2.12	0.95–2.22	1.45	0.94–2.24	5.05	0.28

*Number of exposed cases.

†Hauptmann et al[10] was replaced with Hayes et al,[19] Walrath and Fraumeni,[20] and Walrath and Fraumeni[21] in this analysis because Hauptmann et al did not provide data for all leukemias combined.

‡Includes RRs for all exposure categories combined for each study. Stern et al[72] provided separate data for two tanneries and Dell and Teta[47] provided separate data for salary vs hourly workers.

§Adds the four studies in Bachand et al[6] that were not included in our meta-analysis.

‖Unadjusted data for AML and CML combined were used because adjusted data for both combined were not provided.

χ^2, χ^2 test statistic.

professional workers were 1.38 (95% CI = 0.96 to 1.99; $P = 0.04$) and 2.27 (95% CI = 1.15 to 4.45; $P = 0.009$), respectively. The summary RR of the four studies on myeloid leukemia was 2.47 (95% CI = 1.42 to 4.27; $P = 0.001$). In contrast, in the analysis using only data in which all leukemia subtypes are combined, the summary RR was lower (RR = 1.42; 95% CI = 1.21 to 1.67; $P < 0.001$). In analyses comparing myeloid and lymphatic subtypes using studies and exposure categories where data on both were provided, the summary RR was elevated for myeloid leukemia (RR = 1.55, $P < 0.001$) but not for lymphatic leukemia (RR =

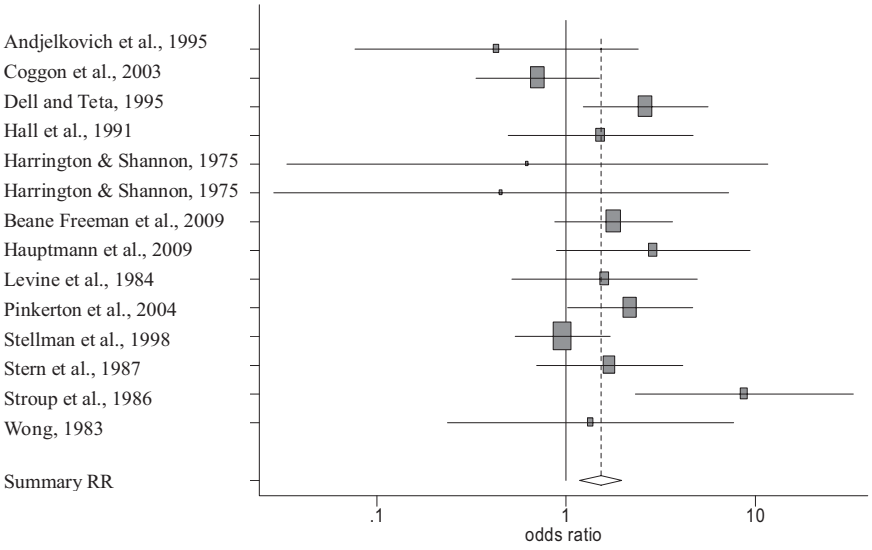

FIGURE 1. Forrest plot of studies used in the meta-analysis of formaldehyde and leukemia.

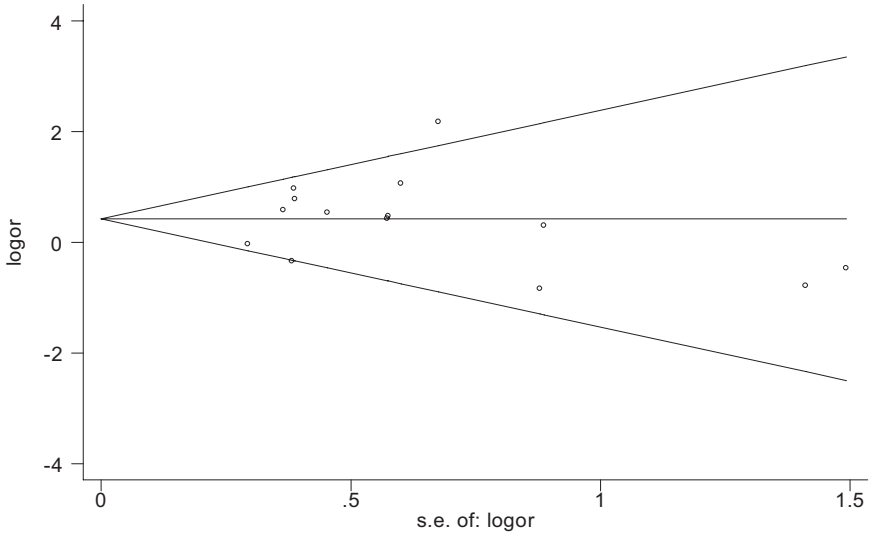

FIGURE 2. Funnel plot of the log odds ratio (logor) versus the standard error (SE) of the log odds ratio of the studies used in the meta-analysis.

0.95, $P = 0.42$; data and methods provided in Supplemental Table 1, http://links.lww.com/JOM/A39).

The RR for the six studies that provided data on a high-exposure group was 1.55 (95% CI = 1.04 to 2.31; $P = 0.016$). In the analysis in which all cohort members are combined into one exposed group (regardless of whether their exposures are high, medium, or low), the summary RR is close to 1.0 (RR = 1.07; 95% CI = 0.86 to 1.32). Adjusting for the healthy worker effect increased the summary RR for all studies and for myeloid studies to 1.72 (95% CI = 1.18 to 2.51) and 2.77 (95% CI = 1.39 to 5.52), respectively.

Sensitivity analyses were conducted to determine the impacts of excluding certain studies. Excluding the Dell and Teta[47] data on research and development workers decreased the summary RR from 1.53 to 1.42 ($P = 0.02$). Excluding the study with the highest RR, Stroup et al,[48] lowered the summary RR slightly, from 1.53 to 1.43 (95% CI = 1.08 to 1.89; data not shown). Neither the Stroup et al nor Dell and Teta studies were included in the high-exposure or myeloid analyses. Including all four studies used in the recent meta-analysis by Bachand et al[6] but excluded here lowered the summary RR from 1.53 to 1.45 ($P = 0.001$).[12,13,25,26]

The funnel plot showed no evidence of asymmetry consistent with publication bias (Fig. 2). Egger's (Kendall's score = −7; $P = 0.74$) and Begg's (bias coefficient = 0.04; $P = 0.96$) tests also showed no evidence of publication bias.

Because dose-response relationships can be an important element of assessing causal inference, we evaluated whether these relationships were present in the individual studies included in this meta-analysis. Table 3 shows the RRs by exposure category for each study that presented dose-response data. In every study except for Coggon et al,[49] there is some evidence that RRs increase as the potential exposure increases. Wong et al had few leukemia cases, although evidence of dose response was seen for all lymphatic and hematopoietic cancers combined.

DISCUSSION

The increased summary RRs of 1.53 ($P = 0.005$) and 2.47 ($P = 0.001$), respectively, provide evidence that formaldehyde is associated with leukemia, specifically myeloid leukemia. The low P values show that these findings are unlikely due to chance. Given the major differences across studies in design, populations, leuke-

TABLE 3. Evaluation of Dose-Response Relationships in Studies of Leukemia and High Exposure to Formaldehyde

Study	Results by Exposure Category				*P* Trend*	Dose Response†
Coggon et al, 2003[49]						
Average exposure (ppm)	Total cohort	>2 ppm				
N	31	8				
SMR	0.91	0.71				No
95% CI	0.62–1.29	0.31–1.39				
Beane Freeman et al, 2009[11]						
Peak exposure (ppm)	0	0.1–1.9	2.0–3.9	≥4		
N	4	14	11	19		
RR	0.82	1.00	1.30	1.78	0.035	Yes
95% CI	0.25–2.67	Reference	0.58–2.92	0.87–3.64		
Hauptmann et al, 2009[10]						
Peak exposure (ppm)	Reference	≤7.0	>7.0–9.3	>9.3		
N	5	9	9	11		
RR	1.0	2.9	2.0	2.9	0.018	Yes
95% CI	Reference	0.9–9.8	0.6–6.6	0.9–9.5		
Pinkerton et al, 2004[71]						
Duration exposed (yr)	<3	3–9	≥10			
N	3	4	8			
SMR	0.83	1.26	2.19			Yes
95% CI	0.17–2.43	0.34–3.23	0.94–4.32			
Stern et al, 1987[72]						
Duration employed (yr)	<1	1–9	≥10			
N	2	2	6			
SMR	0.45	1.00	1.70			Yes
95% CI	0.05–1.68	0.11–3.61	0.63–3.73			
Wong, 1983‡[73]						
Year of hire	After 1960	Before 1961				
N	0	2				
SMR	0	1.35				—‡
95% CI	0–NA	0.15–4.87				

*One-sided *P* values. *P* trends were only provided in these two studies.

†Classified as "Yes" if some evidence of a dose-response relationship was present.

‡In Wong,[73] there were no leukemia cases after 1960, although the expected number was low. SMRs for all lymphatic and hematopoietic cancers by length of employment (<5, 5–9, 10–14, 15–19, 20+ yr) were 0.77, 1.53, 1.64, 1.75, and 2.10, respectively (data by length of employment was not provided for leukemia alone).

N, number of exposed cases.

mia classifications, time periods, and exposure scenarios, some heterogeneity in results are expected. Nevertheless, the relatively low heterogeneity statistics (and the heterogeneity $P > 0.05$) highlight the overall consistency in these data. In the analysis of all studies combined, 9 of the 14 studies (64%) reported RRs >1.0. Three of the five studies with RRs <1.0 involved two or fewer exposed cases each and received little weight (<4%).[50,51] Interestingly, in one of the other remaining two studies, Stellman et al,[52] although formaldehyde exposure outside the wood industry was not associated with leukemia, the combination of work in the wood industry and formaldehyde exposure was associated (RR = 5.79; 95% CI = 1.44 to 23.2).[52] Five of the six studies (83%) reporting data on high-exposure groups had RRs of 1.7 or higher, and all four of the myeloid leukemia studies (100%) had RRs >1.0. Most of the high-exposure studies showed evidence of a dose-response relationship (Table 3).

Summary RRs were elevated in high-exposure studies (RR = 1.55, $P = 0.02$) but were ~1.0 when subjects with high and low exposure were combined into a single exposed group (RR = 1.07, $P = 0.28$). This difference shows the diluting effect that can occur when people with relatively low or no formaldehyde exposure are included in exposed groups. The lower summary RR for lymphatic leukemia (RR = 0.95) when compared with myeloid leukemia (see Supplemental Table 1, http://links.lww.com/JOM/A39) highlights the additional diluting effect that can occur when related and unrelated leukemia subtypes are combined.

This meta-analysis included two recently published large studies. Beane Freeman et al[11] involved 25,619 workers in 10 US formaldehyde-producing or formaldehyde-using plants employed before 1966. Vital status (13,951 deaths) was assessed through 2004 using the National Death Index Plus and other sources, with a median follow-up of 42 years. Exposure for each job held by each worker was evaluated through 1980 using expert assessments involving job titles, tasks, and current and past formaldehyde measurements. For myeloid leukemia, a dose-response trend was seen with increasing peak exposure (Table 3). Similar trends were less clear or not present for average exposure and cumulative exposure, although long intervening periods of low or no exposure can the dilute effects of short-term high exposures when these metrics are used. Myeloid leukemia RRs decreased as the follow-up period increased, which could indicate a relatively short latency

period. The other new study, Hauptmann et al,[10] was a case-control study nested in a large cohort of US funeral workers. Workers were identified through industry associations and licensing boards, and all deaths from lymphohematopoietic malignancies (contributing or underlying) from 1960 to 1986 were collected based on death certificate information from state vital statistics offices. Control subjects ($n = 265$) were randomly selected from funeral workers who died of other causes and matched by sex, dates of birth and death, and data source. Structured interviews with next of kin and coworkers were used to collect information on job history, number of embalmings, and workplace ventilation. Exposure estimates were obtained by linking this information to monitoring data from a previous exposure-assessment study. Despite the small number of myeloid leukemia cases ($n = 34$), statistically significant trends were seen with increasing job duration, average exposure (one-sided $P = 0.029$), and peak exposure (Table 3). Trends were seen for cumulative exposure and number of embalmings, but these were not statistically significant. Increased risks were not seen for other cancer types, suggesting no diagnostic bias. According to the authors, exposure to benzene and radiation were likely to be low in this cohort, and adjustment for smoking had little effect on results. Although some exposure misclassification was likely in this study and in Beane Freeman et al, the misclassification was likely nondifferential with a resulting bias toward the null.[53] Overall, both this study and Beane Freeman et al provided new evidence that formaldehyde is associated with leukemia.

In this meta-analysis, as in almost all meta-analyses of observational epidemiologic data, studies using different exposure metrics (eg, peak exposure, average exposure, and duration) and different exposure categorizations were combined. Because exposure was assessed independently of disease in all studies used in this meta-analysis, misclassification of exposure is likely to be nondifferential, and bias from this is likely to be toward the null and not toward a false association.[53] Similarly, nondifferential misclassification of leukemia status or subtype (eg, misdiagnoses or use of different International Classification of Diseases codes) would also likely cause bias toward finding no effect.

Importantly, the priority order used to choose the exposure metric selected from each study was determined *a priori* and was not based on selecting the highest RR from each study. Combining different exposure metrics can impact RR estimates, but the likely direction of the impact would be to reduce the ability to determine true associations. This is because, if formaldehyde does cause leukemia, some exposure metrics are likely to be more strongly associated with leukemia risks than others.[30,31] In this meta-analysis, we may have included some metrics that are less strongly associated or unassociated with leukemia than others. Including less relevant metrics will dilute summary RR estimates toward 1.0. If every study in this meta-analysis had reported data on the same single metric that was most strongly associated with leukemia risk, it is possible that the true RRs in people with high formaldehyde exposure are even greater than the ones reported here.

The recent meta-analysis by Bachand et al[6] did not find evidence of an association between formaldehyde and leukemia (RR = 1.05 for all leukemia and 1.09 for myeloid leukemia). As seen in Table 4, the major difference with the meta-analysis reported here is our emphasis on high-exposure groups and myeloid leukemia. This resulted in our selecting higher RRs than Bachand et al for several studies. For example, for Beane Freeman et al,[11] we used a RR of 1.78 for myeloid leukemia and peak exposures ≥4

TABLE 4. Comparison of the Current Meta-analysis With the Meta-analysis of Bachand et al[6]

		Current Meta-analysis*				Bachand et al			
Author	**Cohort**	**Exposed group**	**Leukemia**	**RR**	***N***	**Exposed group**	**Leukemia**	**RR**	***N***
Andjelkovich et al, 1995[51]	Iron foundry	Exposed	All	0.43	2	Same*	Same*	0.43	2
Hall et al, 1991[69]	Pathologists	Total cohort	All	1.52	4	Same*	Same*	1.52	4
Harrington and Shannon, 1975[50]	Pathologists	Total cohort	All	0.63	1	Same*	Same*	0.63	1
Harrington and Shannon, 1975[50]	Laboratory technicians	Total cohort	All	0.45	1	Same*	Same*	0.45	1
Levine et al, 1984[70]	Undertakers	Total cohort	All	1.60	4	Same*	Same*	1.60	4
Stellman et al, 1988[52]	US population	Exposed	All	0.96	12	Same*	Same*	0.96	12
Beane Freeman et al, 2009[11]	Formaldehyde industry	Peak 4+ ppm	Myeloid	1.78	19	All exposed	All	1.02	116
Coggon et al, 2003[49]	Chemical plants	Average 2+ ppm	All	0.71	8	Total cohort	Same*	0.91	31
Dell and Teta, 1995[47]	Plastics workers	R and D	All	2.65	8	Not used			
Hauptmann et al, 2009[10]	Embalmers	Peak 9.3+ ppm	Myeloid	2.90	11	Not used			
Pinkerton et al, 2004[71]	Garment workers	Duration 10+ yr	Myeloid	2.19	8	Total cohort	All	1.09	24
Stern et al, 1987[72]	Tannery workers	Duration 10+ yr	All	1.70	6	Total cohort	Same*	0.75†	10
Stroup et al, 1986[48]	Anatomists	Total cohort	Myeloid‡	8.80	3	Same*	All	1.50	10
Wong, 1983[73]	Chemical workers	Employed before 1961	All	1.35	2	Total cohort	Same*	1.18	2
Blair et al, 2001§[25]	Iowa and Minnesota	High exposure	Myeloid	0.68	1	All exposed	All	0.98	64
Partanen et al, 1993[26]	Wood industry	Not used				Same*	Same*	1.40	2
Marsh et al, 2004[17]	Ten US industries	Not used				All exposed	All	0.79	69
Matanoski, 1991[12]	Pathologists	Not used				Total cohort	All	1.35	31
Robinson et al, 1987[13]	Plywood mill	Not used				Total cohort	All	0.59	1

*Same data as used in the current meta-analysis.

†Two relative risks were used: 0.77 from Tannery A and 0.75 from Tannery B.

‡Includes only chronic myeloid leukemia (CML). Data for acute myeloid leukemia (AML) were not provided.

§Not used in the main analysis, but included in a sensitivity analysis. Unadjusted data for AML and CML combined were used because adjusted data for both combined were not provided.

N, number of exposed cases; R and D, research and development; RR, relative risk.

ppm, whereas Bachand et al used a RR of 1.02 for all leukemias combined and any formaldehyde exposure. Importantly, this cohort includes some people who were not highly exposed (eg, not above the current PEL or STEL). In fact, average exposure in this study ranged from 0.01 to 4.3 ppm, cumulative exposure ranged from 0.0 to 107.4 ppm-years, and 71% did not have peak exposures >4 ppm. As discussed, combining people with high and low exposure into a single exposure group and including unrelated leukemia subtypes can both mask true associations.

Other data support the biologic plausibility of the findings linking formaldehyde to leukemia, and these are reviewed in greater detail elsewhere.[7] Briefly, several case-control studies and at least one cohort study have identified links between formaldehyde and nasopharyngeal cancer, providing evidence that formaldehyde is a human carcinogen.[54] A variety of animal studies have also shown increases in cancers, although findings are not consistent across all studies.[54] Cell culture experiments and in vivo studies in human cells and experimental animals have shown that formaldehyde is genotoxic and induces both DNA damage and chromosome changes. Some studies have shown that these effects occur in the lymphocytes of exposed people, although the results of these studies are variable.[55–60] Several mechanisms have been proposed for formaldehyde-caused cancer including direct damage to stem cells in the bone marrow, damage to hematopoietic stem/progenitor cells circulating in the peripheral blood, and damage to the primitive pluripotent stem cells in the nasal turbinates or olfactory mucosa.[7] In a recent study, formaldehyde-exposed workers had reduced white blood cell counts, including decreases in all major myeloid cell types, and increases in leukemia-specific chromosome changes in myeloid blood progenitor cells.[61]

In this meta-analysis, the summary RR was higher for professional workers than industry workers, although the findings for industry workers are not negative. That is, the summary RR in highly exposed industry workers is increased (RR = 1.45) and is unlikely due to chance ($P = 0.04$). In addition, as seen in Table 3, each of the industry studies with dose-response data and sufficient statistical power except for one[49] shows evidence of a dose-response relationship.

The lower summary RR in industry workers is mostly related to a single study, Coggon et al,[49] the only industry study with data on a high-exposure group that reported a RR <1.0. Without this study, the summary RR for high-exposure industry workers (RR = 1.85, 1.20 to 2.86, $P = 0.003$) was closer to that of professionals. The reason why the results of the study by Coggon et al differ is unknown. One factor could be this study's use of average intensity as the exposure metric. It is possible that this metric may be less strongly associated with leukemia risk than peak exposure. This would be true if high-intermittent peak exposures overwhelm detoxification mechanisms to a greater extent than more constant, but lower, average exposures. Indices of average exposure may also underestimate truly relevant exposure in workers with high peak exposures but long intervening periods of little or no exposure. High peak exposures (eg, >STEL of 2 ppm) seem to be more common in professionals than in industry workers.[10,62,63] For example, in Hauptmann et al,[10] estimated peak exposures exceeded 7 ppm in ~70% of the control embalmers and funeral directors. In

TABLE 5. Relative Risks for Other Lymphohematopoietic Cancers in Professionals*

Study	Outcome	RR	95% CI	*N (E)*
Harrington and Shannon, 1975[50]	Hodgkin lymphoma (laboratory technicians)	0	0–NA	0 (1.6)
Walrath and Fraumeni, 1984[21]	Lymphatic leukemia	0	0–NA	0 (2.2)
Walrath and Fraumeni, 1984[21]	Hodgkin lymphoma	0	0–NA	0 (2.5)
Stroup et al, 1986[48]	Hodgkin lymphoma	0	0.0–2.0	0 (1.9)
Harrington and Oakes, 1984[16]	Other LHPM (women)	0	0–18.7	0 (0.16)
Walrath and Fraumeni, 1983[20]	Monocytic leukemia	0.33	0–1.85	1
Logue et al, 1986[74]	Other LHPM	0.48	NA	NA
Harrington and Oakes, 1984[16]	Other LHPM (men)	0.54	0.05–4.29	1
Hauptmann et al, 2009[10]	LHPM-Lymphoid	0.6	0.2–1.3	15
Walrath and Fraumeni, 1983[20]	Non-specific leukemia	0.67	0.01–3.71	1
Stroup et al, 1986[48]	Lymphosarcoma†	0.7	0.1–2.5	2
Hayes et al, 1990[19]	Hodgkin lymphoma	0.72	0.15–2.10	3
Hayes et al, 1990[19]	Lymphatic leukemia	0.74	0.29–1.53	7
Walrath and Fraumeni, 1983[20]	Hodgkin lymphoma	0.87	0.10–3.14	2
Walrath and Fraumeni, 1984[21]	Lymphosarcoma†	0.97	0.19–2.83	3
Walrath and Fraumeni, 1983[20]	Lymphosarcoma†	1.08	0.35–2.52	5
Hall et al, 1991[69]	Hodgkin lymphoma	1.21	0.03–6.71	1
Walrath and Fraumeni, 1983[20]	Other lymphatic	1.23	0.45–2.68	6
Hayes et al, 1990[19]	Non-Hodgkin lymphoma	1.26	0.87–1.76	34
Walrath and Fraumeni, 1984[21]	Other lymphatic	1.33	0.36–3.41	4
Hayes et al, 1990[19]	Multiple myeloma	1.37	0.84–2.12	20
Harrington and Shannon, 1975[50]	Hodgkin lymphoma (pathologists)	1.43	0.02–7.95	1
Walrath and Fraumeni, 1983[20]	Lymphatic leukemia	1.54	0.41–3.94	4
Stroup et al, 1986[48]	Other lymphatic	2.0	0.7–4.4	6
Hayes et al, 1990[19]	Other leukemia	2.28	1.39–3.52	20
Walrath and Fraumeni, 1984[21]	Other leukemia	2.86	0.77–7.32	4
Walrath and Fraumeni, 1984[21]	Monocytic leukemia	6.67	0.75–24.1	2

E, expected number of cases; LHPM, lymphohematopoietic malignancy; *N*, observed number of cases; NA, not available.
*Includes RRs for all reported types lymphohematopoietic cancers that do not include myeloid leukemia. Levine et al[70] did not report on other subtypes.
†Includes lymphosarcoma and reticulosarcoma (ICD-8 codes 200).

contrast, peak exposures exceeding 4 ppm were seen in only 24% of all subjects in the large National Cancer Institute cohort study of formaldehyde industries.[18] Given these data, the higher summary RR seen in professionals compared with industry workers is consistent with the hypothesis that peak exposure is an important metric in determining leukemia risk.

Another reason why the results of the study by Coggon et al are different from other studies may be because that they combined all leukemia subtypes, including leukemias of unspecified cell type (International Classification of Diseases-9 code 208). These unspecified leukemias can account for 25% of all leukemias and were not included in other studies used in our meta-analysis.[64] As discussed, the inclusion of unrelated leukemia subtypes can dilute summary RRs toward 1.0.

There are other possible reasons why summary RRs are lower in industry workers, but these seem unlikely. One possibility is confounding by some other agent (eg, benzene, radiation, or viruses) in professionals. Nevertheless, funeral directors, embalmers, and anatomists are not known to be exposed to benzene or radiation levels associated with >2-fold increased risks of myeloid leukemia.[65,66] In addition, a recent International Agency for Research on Cancer working group concluded that there was little evidence that professionals have more viral infections or that viruses cause myeloid leukemia.[54] Other factors including pesticides, chemotherapy agents, electromagnetic fields, or inherited disorders have also been linked to leukemia[67,68] but are unlikely to be prevalent enough or strongly enough related to formaldehyde exposure to cause substantial confounding.

Another reason why summary RRs are higher in professionals than in industry workers may be a diagnosis bias; that is, myeloid leukemia could be more likely to be diagnosed in professionals who may have higher quality medical care than industry workers.[6] If this were true, it would be expected that RRs for other lymphopoietic cancers would also be increased in professionals. Table 5 shows RRs for all lymphopoietic cancer types not including myeloid leukemia in all the studies of professionals reviewed for this meta-analysis. Most of these RRs are <1.0 (15 of 27) and only three (11%) are >2.0. This suggests that diagnostic bias is unlikely to have caused the summary RR of 2.27 identified for formaldehyde-exposed professionals in this meta-analysis.

In this meta-analysis, excess summary RRs increased by ~25% after adjusting for the healthy worker effect. Although the impact of this bias has been well described for all-cause mortality, its role in cancer mortality is less well documented. To evaluate this, all-cause and all-cancer SMRs were collected from all studies on formaldehyde and lymphohematopoietic cancer reviewed for this meta-analysis (see Supplemental Table 2, http://links.lww.com/JOM/A40). Twenty-nine of the 34 all-cause SMRs (85.3%; average SMR = 0.86) and 26 of 36 all-cancer SMRs (72.2%; average SMR = 0.89) were <1.0. All-cancer SMRs would probably be even lower if occupationally caused cancers, including some lung cancers and some leukemias, were excluded. Overall, the general trend for all-cancer SMRs being <1.0 provides some evidence that the healthy worker effect is affecting cancer rates in many of these studies.

CONCLUSIONS

In summary, the findings of this meta-analysis suggest that formaldehyde exposure is associated with increased risks of leukemia, particularly myeloid leukemia. These findings also highlight the importance of focusing on high-exposure groups and myeloid leukemia when evaluating the human carcinogenicity of formaldehyde. Although confounding, publication bias, diagnostic bias, or substantial exposure or outcome misclassification cannot be completely ruled out, our evaluations suggest that these biases are unlikely causes of the associations identified. Despite the overall evidence of an association, some inconsistencies remain, including the RR <1.0 reported in the large Coggon et al[49] study. Future research is needed to explain these inconsistencies and to elucidate the possible mechanisms of formaldehyde carcinogenicity, the role of short-term peak versus long-term average exposures, and the possible impacts of low environmental exposures.

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