

CORRESPONDENCE

Re: Mortality From Lymphohematopoietic Malignancies Among Workers in Formaldehyde Industries

The study described in the article by Hauptmann et al. (1) has several strengths, including large size, long follow-up, and attempts to control for potentially important confounding factors. However, the study does not provide conclusive evidence of a causal association between formaldehyde exposure and leukemia for several reasons. In particular, the large relative risks (RRs) reported for the internal comparison stratified by exposure category need to be reconciled with the external compar-

isons in which the standardized mortality ratio (SMR) for all lymphohematopoietic neoplasms in formaldehyde-exposed workers is 0.8 (95% confidence interval [CI] = 0.7 to 0.9). We have estimated SMRs for leukemia and other lymphohematopoietic malignancies for the peak formaldehyde exposure categories shown in table 3 of Hauptmann et al. (1). These SMRs (Table 1) suggest that mortality from lymphohematopoietic malignancies is not higher than would be expected in those workers with a peak formaldehyde exposure of 4 ppm or more, but rather is lower than would be expected in workers in the lowest exposure category of less than 2 ppm (SMR = 0.6, 95% CI = 0.4 to 0.7). Similar conclusions may be drawn from the leukemia findings.

Additionally, we point out that the assignment of peak exposure was based primarily on professional judgment, not on actual measurements. Such an assignment makes this exposure the weak-

est of the four exposure metrics used in the study by Hauptmann et al. (1) relative to supporting data, and this exposure is typically the most difficult exposure metric to estimate in the absence of detailed measurements.

Hauptmann et al. (1) briefly discuss the biologic evidence relevant to their hypothesis of formaldehyde-induced lymphohematopoietic cancer, but they conclude that the evidence is inconsistent. However, this conclusion is in conflict with substantial experimental data showing that, under controlled exposures, there is no increase in the concentration of formaldehyde in the blood of humans (2 ppm), monkeys (6 ppm), or rats (15 ppm) (2,3) and that formaldehyde does not appear to induce cancer via inhalation at sites other than the respiratory tract (4). These results strongly suggest that inhaled formaldehyde is rapidly metabolized in the respiratory tract, does not reach the bone marrow, and is therefore unlikely to induce distant-site toxicity including leukemia.

Finally, discrepancies in the data from available industrial studies suggest that the findings of Hauptmann et al. (1) may be due to chance, some uncontrolled confounding exposure, or an inappropriate comparison group. For example, a large study of workers exposed to formaldehyde in the U.K. (5) reports no increased risk for leukemia in the entire study cohort (SMR = 0.9, 95% CI = 0.6 to 1.3) or among workers with the highest formaldehyde exposures (SMR = 0.7, 95% CI = 0.3 to 1.4).

Thus, we believe that the findings of Hauptmann et al. (1) need to be critically assessed in light of external comparisons, existing biologic evidence, the findings of other studies, and a more complete understanding of the exposure metrics and classification parameters used. Until these issues are meaningfully addressed, questions will continue to be raised about the overall significance of the findings reported.

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Table 1. Estimated standardized mortality ratios (SMRs) for selected lymphohematopoietic cancers by formaldehyde peak exposure*

Categories of formaldehyde peak exposure, ppm (ICD codes)	No. of observed deaths	SMR (95% CI)	RR (95% CI)
Lymphohematopoietic tissue (ICD 200–209)			
Not exposed	17	0.62 (0.36 to 0.99)	1.08 (0.60 to 1.94)
>0–<2.0	48	0.55 (0.41 to 0.73)	1.00 (referent)
2.0–<4.0	49	0.94 (0.70 to 1.25)	1.71 (1.14 to 2.58)
≥4.0	64	1.03 (0.79 to 1.32)	1.87 (1.27 to 2.75)
Non-Hodgkin lymphoma (ICD 200, 202)			
Not exposed	5	0.52 (0.17 to 1.22)	1.12 (0.38 to 3.31)
>0–<2.0	15	0.52 (0.29 to 0.85)	1.00 (referent)
2.0–<4.0	14	0.72 (0.39 to 1.20)	1.39 (0.67 to 2.91)
≥4.0	15	0.64 (0.36 to 1.05)	1.23 (0.59 to 2.55)
Hodgkin disease (ICD 201)			
Not exposed	1	0.37 (0.01 to 2.06)	0.51 (0.06 to 4.52)
>0–<2.0	5	0.60 (0.19 to 1.39)	1.00 (referent)
2.0–<4.0	7	2.06 (0.83 to 4.24)	3.45 (0.98 to 12.16)
≥4.0	8	2.00 (0.86 to 3.94)	3.35 (0.97 to 11.59)
Multiple myeloma (ICD 203)			
Not exposed	5	1.23 (0.40 to 2.85)	2.10 (0.66 to 6.75)
>0–<2.0	9	0.66 (0.30 to 1.26)	1.00 (referent)
2.0–<4.0	8	0.98 (0.42 to 1.92)	1.48 (0.56 to 3.92)
≥4.0	11	1.10 (0.55 to 1.97)	1.67 (0.68 to 4.12)
Leukemia (ICD 204–207)			
Not exposed	4	0.38 (0.10 to 0.98)	0.78 (0.25 to 2.43)
>0–<2.0	16	0.49 (0.28 to 0.80)	1.00 (referent)
2.0–<4.0	20	1.01 (0.61 to 1.55)	2.04 (1.04 to 4.01)
≥4.0	29	1.21 (0.81 to 1.74)	2.46 (1.31 to 4.62)

*Standardized mortality ratios for unexposed workers are given in table 2 of Hauptmann et al. (1), and observed numbers of deaths and relative risks are given in table 3 of (1). We estimated standardized mortality ratios for exposure subcategories from the data in (1). Estimates were obtained by setting standardized mortality ratios equal to relative risks, subject to the constraint that the expected number of deaths in the exposure subcategories sum to the expected number of deaths for all exposed workers [derived from table 2 of (1)]. The form of age standardization used in standardized mortality ratio calculations and Poisson regression procedures is different, and the true standardized mortality ratio (if calculated by the study authors) will not be exactly the same as those estimated but will likely be similar. CI = confidence interval; RR = relative risk derived from Poisson regression analysis; ICD = *International Classification of Diseases*, 8th revision.

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NOTES

M. Casanova and H. d'A. Heck have served as consultants to the Formaldehyde Epidemiology, Toxicology, and Environmental Group. P. Cole currently conducts research sponsored by the Formaldehyde Council. R. Leonard is currently employed by DuPont Haskell Laboratory, a business unit of E. I. DuPont de Nemours and Co., which produces and uses formaldehyde. R. Lewis is currently employed by Solutia Inc., which produces and uses formaldehyde. G. M. Marsh has received funding from Cytec Industries for research relating to nasopharyngeal carcinoma and formaldehyde but not for lymphohematopoietic malignancies and formaldehyde. M. G. Ott is employed by BASF Corp., a user of formaldehyde in the United States, and holds stock in BASF AG, a manufacturer and user of formaldehyde outside the United States.

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RESPONSE

We agree with Casanova et al. that our study (1) does not provide conclusive evidence of a causal association between formaldehyde exposure and leukemia. However, it is difficult to conceive how our findings of an increasing

risk of lymphohematopoietic malignancies, especially leukemia, with increasing average intensity and peak levels of exposure to formaldehyde could be explained solely by bias due to imprecision of exposure metrics or uncontrolled confounding, in the absence of a causal association.

The availability of the peak exposure metric is a unique feature of our study, and peak exposure is the metric that best characterizes exposure patterns similar to those experienced by pathologists and embalmers (2), for whom increased leukemia mortality has been observed in several studies (3–5). Estimates of peak exposure were based on the judgment of experts using information on job titles and tasks in combination with measurements of formaldehyde concentrations at selected workplaces. Uncertainties in estimating levels of peak exposure are unlikely to have induced the observed exposure–response gradient because the assessment was done before determining vital status and cause of death and was therefore unlikely to be differential with respect to disease outcome. We also observed increasing risks for average exposure intensity and duration of exposure, although not for cumulative exposure.

Confounding from unobserved factors is always a possibility in observational studies. Benzene is the only established risk factor for leukemia that could confound our analysis at a level sufficient to explain our results. However, after we excluded all 586 workers (2% of the cohort) with potential exposure to benzene from the analysis, we still observed an association between levels of peak exposure and leukemia.

We disagree with Casanova et al. that external comparisons are the method of choice for an exposure–response evaluation when there is an adequate reference group within the study population. Other workers are the best comparison group because of the healthy worker bias associated with standardized mortality ratios (SMRs). Even though the overall reduced SMR for leukemia is interesting, the patterns of increasing risk with increasing measures of exposure, as seen for both relative risks and SMRs, are the most important element in support of an exposure–response relationship.

Biologic explanations for formaldehyde effects beyond the upper respiratory tract are uncertain. However, there is evidence that genotoxic effects of inhaled formaldehyde can be detected *in vivo* in the bone marrow of rats and in human peripheral lymphocytes [cited in (1)].

We agree that our findings could be due to chance. However, chance could also explain the failure to see an association between formaldehyde exposure and leukemia mortality in a British cohort study (6) that included approximately half as many leukemia deaths as in our study. Increased mortality from leukemia was observed among textile workers (7), pathologists (3), and embalmers (4,5) exposed to formaldehyde. Many questions remain about possible links between formaldehyde exposure and risk of lymphohematopoietic malignancies, and we support further epidemiologic, toxicologic, and mechanistic research.

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