Comments on the National Toxicology Program Draft Background Document for Formaldehyde

A Meta-Analysis of Formaldehyde Exposure and Risk of Leukemia and Nasopharyngeal Cancer

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The following comments are based on a new meta-analysis of the epidemiological evidence pertaining to occupational formaldehyde exposure and the risks of leukemia and nasopharyngeal cancers.[1]

Background

In 2006, the International Agency for Research on Cancer (IARC) classified formaldehyde as carcinogenic to humans (IARC, 2006). In Monograph 88, IARC decided that the epidemiologic evidence available was strong but not sufficient to conclude that formaldehyde specifically causes leukemia in humans. However, IARC noted that studies reporting excess mortality from nasopharyngeal cancer (NPC) provided sufficient evidence of formaldehyde's carcinogenicity, thus providing the basis for the labeling of formaldehyde as carcinogenic. The NPC results were based primarily on the statistically significant excess of NPC deaths among industrial workers exposed to formaldehyde in a large US cohort.

The objective of our meta-analysis was to use the available literature to evaluate the hypothesis that occupational formaldehyde exposure was associated with an increased risk of leukemia or NPC. An additional goal was to conduct a series of sensitivity analyses not previously considered to provide possible alternative explanations for the associations reported in several studies between formaldehyde exposure and NPC and leukemias.

Methods

Standard meta-analytic methods were used for study selection, data extraction, inter-study heterogeneity investigations and summary risk estimation. Since very

[1] Bachand A, Mundt KA, Mundt DJ and Montgomery, RR. Epidemiological Studies of Formaldehyde Exposure and Risk of Leukemia and Nasopharyngeal Cancer: A Meta-Analysis. *Critical Reviews in Toxicology* (accepted for publication).

few case-control or cohort studies reported risk estimates (REs) for specific exposure categories, and exposure was categorized differently among the studies, we only used REs that compared exposed versus unexposed persons. When no overall effect estimate was reported, we calculated a weighted average of the category specific risk estimates. In one re-analysis of NCI data (Marsh, G. M., et al., 2007b) where only results for continuous and highest peak exposures were presented, we used the highest peak exposure. We considered certain occupations as proxy measures for formaldehyde exposure, recognizing that many jobs would involve other exposures as well. These occupations included embalmers, undertakers, funeral directors, pathologists, anatomists, radiologists, laboratory technicians, foundry workers, chemical manufacturers, plastics manufacturers, plywood workers, leather tanners, and garment workers.

The outcomes of interest were leukemia and nasopharyngeal cancer morbidity or mortality. Age, gender, socioeconomic status (SES), smoking, alcohol consumption, pesticide exposure, study location (local variations compared to national rates), study region (US/Canada, Europe or Asia) and calendar year were considered as potential confounders. Additionally, we investigated the effect on the study results of job type (professional vs. industrial/technical), publication time period, and sources of cases and controls (for case-control studies only).

We conducted searches of PubMed and ToxNet (Toxline) for all human epidemiological studies on formaldehyde and cancer that were written in English, as well as additional internet sites and citations in published documents. A total of 283 abstracts were screened, with a study being excluded because it: [1] was not an epidemiological study; [2] did not focus on formaldehyde; [3] focused on an outcome other than cancer; or [4] did not present results for NPC or leukemia. Seventeen studies of leukemia and eighteen studies of nasopharyngeal cancers were included in the final meta-analyses.

Although previous reviews and meta-analyses have included them, we excluded studies reporting proportionate mortality ratios due to the well-recognized limitations such as their lack of ability to account for person-time at risk and dependence on mortality rates for irrelevant causes of death within the study population. Studies that reported no exposed cases also were excluded from the meta-analyses. No studies were excluded for lack of control for confounding.

All analyses were conducted separately for leukemia case-control and cohort studies and for NPC case-control and cohort studies.

We created separate forest plots (illustrations of the magnitude and precision of the effect estimates) and funnel plots (evaluations of publication bias) for leukemia and NPC. Heterogeneity among effect estimates was investigated using regression models and normal quantile plots. We used Q-test results from fixed effects and random effects regression to assess evidence of heterogeneity

among all studies within subgroups of studies. If there was no evidence of heterogeneity among studies, we calculated and compared summary REs from fixed-effect and random-effects regression. Weights were based on estimated standard errors (SEs). We conducted sensitivity analyses to investigate the potential influence of exposure and outcome definitions, different case and control sources and job type on the meta-analysis results. We also investigated the potential effects of confounding variables.

Results

Leukemia

For cohort studies, REs ranged from 0.43 to 1.60, and all but one 95% confidence interval included 1. Neither case-control REs was statistically significant. Based on the funnel plot, no evidence of publication bias was seen, and the normal quantile plots suggested normality and homogeneity among studies. Results from fixed and random effects regression were identical, so only fixed effect results are presented.

The overall leukemia RE was 1.05 (95% CI: 0.93, 1.20), with similar results when the meta-analysis was restricted to specific leukemia types. The summary RE for professional and technical workers was 1.28 (95% CI: 0.98, 1.66) and for industrial workers the RE was 0.99 (95% CI: 0.86, 1.15). Excluding studies with only one case had little effect on the results.

Nasopharyngeal cancer

For cohort studies, most 95% CIs included unity. The three highest REs were observed in primary studies that were restricted to or included Plant 1 of the NCI cohort, a subset known to have unusually high REs for the association between formaldehyde and NPC (Marsh, G. M., et al., 2007a). For case-control studies, all 95% CIs included 1.

The normal quantile plot for cohort studies did not perfectly follow a straight line suggesting some evidence of heterogeneity among studies, which was attributed to the inclusion of results for Plant 1. The normal quantile plot for case-control studies followed a straight line with the exception of one study whose population came from Plant 1 of the NCI cohort, which had an unusually high median unbiased estimate of the odds ratio.

Results from fixed and random effects regression were identical, therefore only results from the fixed effects analysis are presented. The overall RE for case-control studies was 1.22 (95% CI: 1.00, 1.50). The RE for cohort studies, excluding NCI Plant 1, was 0.72 (95% CI: 0.40, 1.29). All but one primary cohort study included in our meta-analysis reported an SMR less than 1. We found no statistically significant differences between subgroups by study location or SES; however, studies that did not adjust for smoking showed a 30% statistically

significant increase in risk, while the studies that adjusted for smoking showed a smaller summary RE and the 95% CI included 1. Excluding studies with only one case had little effect on any of the results.

The results for NPC cohort studies were based on the SMR from Marsh 2005 (Plants 2-10) to represent the NCI cohort. Including REs based on data from plant 1 in the meta-analysis had a considerable effect on the results. The SMR for Plant 1 was about 10 times as great as the next largest RE from any study not containing Plant 1. When we included the Plant 1 SMR in the meta-analysis, the overall summary RE increased from 0.72 to 1.60 and the stratum-specific summary RE was inflated in whichever stratum the anomalous SMR fell. The overall Q-test p-value was <0.0001, indicating that including Plant 1 led to significant heterogeneity among studies, and the estimation of summary REs was not appropriate.

Conclusions

Our meta-analyses considered the most recent studies investigating the association between formaldehyde and leukemia or NPC, including the 2009 NCI update, which is a large, well-conducted study, but was published too recently to have been included in previous meta-analyses or reviews.

For leukemia, we found no support for an association among industrial workers, believed to be the most likely exposed to higher concentrations of formaldehyde for sustained periods, confirming previous meta-analyses by Collins and Lineker (2004) and Bosetti et al. (2008). Like Collins and Lineker (2004), we found that leukemia REs were higher in studies published prior to 1995, but only among studies of professional workers.

For NPC, we found no overall increase in risk after excluding Plant 1 of the NCI cohort, confirming an earlier finding by Bosetti et al. We also found evidence that failure to adjust for smoking may have affected some of the primary study results.

In conclusion, our meta-analysis on formaldehyde exposure and NPC suggests that the reported association between the two may have been driven by results from a single anomalous production plant and possibly uncontrolled confounding due to smoking. Our meta-analysis on formaldehyde exposure and leukemia demonstrates there is little evidence of a consistent relationship, and that the overall increased risk previously reported was driven by PMR studies. Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukemia.

References

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