Comments on the Draft Background Document on Formaldehyde Exposure and Risk of Cancer

James J. Collins, Ph.D.
Director of Epidemiology
The Dow Chemical Company
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On behalf of The Dow Chemical Company

This Draft Background Document includes the major epidemiology studies which examine cancer risk and exposure to formaldehyde. The authors have done a good job assembling the information. The Draft Background Document also has focused on the NCI study as being one of the more important studies because of it size.(1, 2) It is the largest of the cohort studies in terms of number of workers exposed to formaldehyde and the number of person years of exposure. However, another important study is the British Industry Wide study which should also be featured.(3) The British Industry Wide cohort study has the highest estimated worker exposures.(3) For example, the British Industry Wide study reports 28% of the workers having TWA exposure exceeding 2 ppm compared to only 4% in the NCI study. While size is an important consideration for causal assessment, so are exposure levels. Study power when examining exposure-response is based both on size and exposure level. Thus the NCI study and the British Industry-wide study should be jointly featured when discussing results and we believe the results from these studies should be reported in every section of the site specific results. Another large cohort study that also might be featured in every section is the NIOSH

Garment Workers study although this study has no exposure estimates, unlike the other two cohort studies.(4)

The authors should make a distinction between exposures in the case-control and cohort studies. It has been argued that cohort studies have much higher exposure levels than the case-control studies since high exposure to formaldehyde is relatively rare. As Bosetti et al. point out "most case-control studies were community-based, and had no formaldehyde workers nor direct measure of formaldehyde exposure, but rather classified workers primarily by their job titles, using ad hoc exposure matrices."(5) This makes the exposure estimates in the case-control studies much more uncertain and almost certainly lower in most cases than the cohort studies.(6) Also, when reporting the meta-analyses results, it would be helpful to stratify the data by cohort studies and case control studies. When the Draft Background Document reports the results for meta-analyses, both cohort and case-control studies should be reported separately.

There have been several meta-analyses of the epidemiology studies examining the relationship between cancer risk and formaldehyde exposure.(6-9) These meta-analyses use similar approaches as recommended for meta-analyses examining the overall risk from disease and exposure and evaluating exposure response for each study.(10) The recent meta-analysis done by Zhang and colleagues, however, violate these rules and only examines the relative risks from high exposed groups. This unconventional approach thus fails to examine the exposure-response in each of the studies, a key concept in evaluating causality. It is also not clear how Zhang and colleagues selected the highest exposure

group. If it was done based on highest relative risks, this might introduce serious bias into the estimates of the meta-relative risks. The Draft Background Document should point out these limitations.

We also have comments on each of the cancer specific sections as follows:

Sinonasal Cancer

The category, "sinonasal cancer" used in most studies, combines nasal cavity cancers and nasal sinus cancers into a single category. The experimental studies on rats and mice both show excesses of nasal cavity cancer at high exposure levels with no mention of the nasal sinuses. Formaldehyde, however, does not penetrate into the nasal sinuses in rats and non-human primates where most of the human "sinonasal cancers" occur.(11) Ninety percent of the "sinonasal cancers" in humans are of the sinuses and not of the nasal cavity.(12) It would be more informative if studies examined only nasal cavity cancer, but few studies have done this. Virtually, all of the studies in this Draft Background Document use the category "sinonasal cancers" which would may bias the relative risk estimates. The Draft Background Document should discuss this.

The meta-analyses indicate that there is no increased risk of sinonasal cancer in the cohort studies.(5, 6) The case-control studies, however, in the meta-analyses do demonstrate an increased risk for this cancer.(6, 8) Many of the case-control studies on sinonasal cancer also report exposure to wood dust as a potential confounding exposure. One meta-analysis stratified the high wood dust studies from the low wood dust studies

and found the increased sinonasal cancer risk only occurred among the high wood dust study workers.(6) The potential for confounding with wood dust should be acknowledged in the Draft Background Document.

Nasopharyngeal Cancer

The NCI study is heavily relied upon for showing increased rates of nasopharyngeal cancer (NPC) related to formaldehyde levels.(13) This study also reports exposure-response relationships with some of the exposure estimates relied upon in the study. There are two other cohort studies mentioned that report more NPCs observed than expected but both of these studies are relatively small.(14, 15) The authors also mention the British Industry wide study which reports only 1 observed NPC.(3) No expected deaths are provided in this study but it is clear that 1 observed case is less than the expected cancers.

Relying on the NCI study reporting the NPC excess as the basis for a relationship with formaldehyde exposure may be problematic. Beane-Freeman and colleagues from the NCI report that the NCI study reporting the NPC excess was missing 1,006 deaths that should have been included.(1, 13) These additional deaths would have increased cohort mortality by 10.5% in the Hauptmann et al. study.(13) These additional deaths for such rare cancer like NPC may have increased death rates in both exposed and unexposed workers, possibly attenuating the exposure-response. This missing information in the Hauptmann et al. may call into question the validity of the findings. We suggest the

authors of the Draft Background Document discuss this limitation of the NCI study on NPC study.

Evaluation of NPCs in the cohort studies is difficult because of incomplete reporting of expected numbers when there are no or few observed NPCs such as in the British Industry-Wide study.(3) In addition, most studies fail to report expected numbers of NPCs when there are no observed NPC. Thus in meta-analysis, expected number of NPC would be underreported leading to an over-estimatation of the relative risk. The authors report the meta-relative risk (mRR) from just the studies reporting observed and expected deaths to be 1.3 (95%CI = 0.6-2.5).(5, 6) However, when this underreporting of this rare cancer is taken into account, there is no increase in NPC deaths compared to expected deaths (mRR = 1.0, 95%CI 0.5-1.8).(6) The authors of the Draft Background Document should report this limitation of most meta-analyses.

The methods for developing the exposure estimates used in the NCI study have been described.(16, 17) According to these studies, there were no actual measures of peak exposure to formaldehyde. This peak exposure metric is associated with NPCs, all leukemias, and myeloid leukemia in the NCI studies. Further, the highest peak exposure metric used by the authors is unconventional and difficult to interpret. In their exposure-response analysis of the highest peak exposure, the authors treat peak exposure as a time-dependent variable. As workers experience different peak exposures over their career, they are allocated to the highest peak exposure category experienced.(18) Thus, it is possible for a worker to have reached their highest peak during their first day of

exposure, receive very little exposure the remainder of their work history, then die and be assigned to the category associated with this single, early peak. Conversely, a worker could have received very little exposure up to a point close in time to their death date, then experience a similar high peak. This worker would end up in the same peak category as the first example. Many other feasible exposure scenarios could easily be described that would result in workers being assigned to the same category under very different patterns of exposure. Defining the peak exposure metric, as the authors have, potentially groups very different exposures into similar categories and makes interpretation difficult.

The Draft Background Document fails to mention that 6 of the 8 NPCs among formaldehyde exposed workers in the NCI study occur at a single plant and there is no NPC excess or exposure response when the remaining 9 plants are examined excluding the one plant.(19) Recently, the workers from this plant who died of NPC were assessed for other potential exposures in previous employment with the conclusion that the excess in NPC at this plant which clearly drives the results of the NCI study may be due to exposures to metal processing and not to formaldehyde.

Lymphohematopoietic Cancers

The limitations of exposure estimates based on peak exposure in the NCI study have been discussed previously. The NCI authors in the current update also employ a more conventional measure of peak exposure, the number of peaks above 4.0 ppm.(1) This measure has the advantage of grouping similarly exposed workers in the same exposure

category unlike the previously described measure of highest peak exposure. The NCI has used this measure previously to examine cancer risk,(20) the NCI collected the number of peaks above 4.0 ppm specifically for this study,(17) and other studies examining leukemia risk from occupational exposures have used a similar metric.(21, 22) The Draft Background Document should discuss this use of the more conventional measure and how the different measures of peak exposure produce different findings.

The Draft Background Document attempts to interpret the risks and exposure-response trends for all lymphatic and hematopoietic cancers (LHP). The LHP are a grouping of many cancers each with a distinct etiology and risk factors.(23) While we agree that there is an advantage to examining specific cancers in this LHP category, we see little value in using this entire category to assess causality. It is unwarranted and biologically implausible to assume that formaldehyde would be capable of causing every known type of LHP malignancy.

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