Comments on

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Draft Background Document for
Formaldehyde

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by

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Introduction

My name is Gary Marsh. I received my Ph.D. in Biostatistics in 1977 from the University of Pittsburgh, Graduate School of Public Health, and in 1997 became a Fellow of the American College of Epidemiology. Currently, I am Professor and Interim Chairman of the Department of Biostatistics and Director of the Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. I have devoted my 32-year research-oriented career at the University of Pittsburgh to methodological development and field applications in the areas of occupational biostatistics and epidemiology.

Rationale and Basis of Comments and Conclusions

I am pleased to present, on behalf of the Formaldehyde Council, Inc. (FCI) and Georgia-Pacific Chemicals LLC, comments and conclusions related to NTP's proposed nomination of formaldehyde to the *12th Report on Carcinogens (RoC)*. My comments focus on the National Cancer Institute's (NCI) ongoing cohort study of formaldehyde-exposed workers, my reanalyses of data from the NCI study, my independent epidemiology study of one of the 10 plants included in the NCI study (Plant 1) and the International Agency for Research on Cancer's (IARC) 2004 decision to reclassify formaldehyde as a Group 1 (known human carcinogen). The NCI cohort study and 2004 IARC reclassification represent a substantial portion of the available epidemiological information that NTP will rely upon as they consider nominating formaldehyde for the *12th RoC*.

The comments that follow provide support for my conclusion that questionable, non-robust, and in some cases, incorrect NCI study results for leukemia and nasopharyngeal cancer mortality were used by the International Agency for Research on Cancer (IARC) to make inappropriate and misleading decisions regarding human cancer risk from formaldehyde exposure, namely their 2004 reclassification of formaldehyde as a Group 1 (known human carcinogen) (IARC, 2006). My conclusion is supported by several reanalyses of the NCI cohort data and an independent cohort study of one of the 10 NCI study plants (conducted by my research group at the University of Pittsburgh) and the 2009 release by NCI of corrected analyses from their 1994 cohort follow-up. These new results have cast considerable doubt on the scientific validity of NCI's findings and IARC's 2004 reclassification.

The following sections describe key findings from the NCI cohort study and details about the University of Pittsburgh reanalyses and independent cohort study that provide the basis of support for my conclusion.

The NCI Cohort Study (1994 Follow-Up) and The University of Pittsburgh Reanalyses

The NCI cohort mortality study comprises 26,651 industrial workers employed before 1966 in one or more of 10 formaldehyde-producing or -using facilities in the United States. In 1986, NCI published the results of the original 1984 follow-up (Blair et al., 1986; 1987; 1990; Stewart et al., 1987). This original report revealed some evidence of elevated mortality risks for NPC that were concentrated in one study plant located in Wallingford, CT (NCI Plant No. 1), but no evidence of elevated risks from leukemia or other lymphohematopoietic malignancies. In 2003 and 2004, NCI published two papers on a 1994 follow-up of the cohort, one focused on mortality from lymphohematopoietic malignancies (Hauptmann et al., 2003) and one focused on NPC (Hauptmann et al., 2004).

NCI Findings for Leukemia

Key findings in the 2003 NCI report (Hauptmann et al., 2003) included an unexpected suggestion of a causal association between formaldehyde exposure and mortality from leukemia, particularly myeloid leukemia. The suspected associations for leukemia and myeloid leukemia were based exclusively on internal mortality rate comparisons (via relative risks (RR)) and were observed for only two of four formaldehyde exposure metrics considered, namely, highest peak formaldehyde exposure and to a lesser extent, average intensity of formaldehyde exposure (AIE). NCI's internal analyses showed no relationship of the risk of leukemia or of myeloid leukemia with cumulative formaldehyde exposure or with duration of formaldehyde exposure. The authors of the NCI report concluded, *"The exposure-response gradient observed and the consistency with other epidemiological studies in occupations with formaldehyde exposure and some experimental studies suggest a causal association between formaldehyde exposure and leukemia." (Hauptmann et al., 2003, page 1622)*.

University of Pittsburgh Reanalysis of NCI Leukemia Data

In 2004, we performed an extensive reanalysis of the NCI cohort data file to determine whether the NCI's suggestion of causal associations between formaldehyde exposure and mortality from leukemia and myeloid leukemia were robust with respect to alternative characterizations and categorizations of formaldehyde exposure and to alternative methods of data analysis (Marsh and Youk, 2004). Using the detailed cohort data provided to us by NCI, we computed U.S. and local county rate-based standardized mortality ratios (SMRs) and internal cohort rate-based relative risks (RR) by categories of four formaldehyde exposure metrics (highest peak, average intensity (AIE), cumulative and duration), using both NCI categories and an alternative categorization based on tertiles of deaths from all leukemia among exposed subjects.

For highest peak exposure, we computed RRs by the duration of time worked in the highest peak category and the time since highest peak exposure. For AIE, we computed RRs by the duration of exposure and the time since first exposure. Our external comparisons revealed that the elevated leukemia and myeloid leukemia RRs and associated trends reported by NCI for highest peak and AIE occurred because null (or slight) to moderate mortality excesses were compared with statistically significant baseline category deficits in deaths. Our alternative categorization of AIE yielded leukemia and myeloid leukemia SMRs close to 1.00 in the highest exposure category, and revealed weaker evidence of a trend in RRs for leukemia and myeloid leukemia.

We corroborated NCI's finding of no association for cumulative and duration of formaldehyde exposure. We found no consistent evidence that leukemia or myeloid leukemia risks increased with increasing duration of time spent in a given highest peak exposure (or for AIE, duration of exposure in a given AIE category). We also found no consistent evidence that leukemia or myeloid leukemia risks were greater in the more relevant shorter (less than 20 years) versus longer (20 + years) periods of time from the first highest peak exposure (or for AIE, first exposure).

We concluded that our reanalysis of the NCI cohort data provided little evidence to support NCI's suggestion of causal associations between formaldehyde exposure and mortality from leukemia and myeloid leukemia. NCI's key findings for highest peak exposure and AIE did not adequately account for the inordinately large deficits in deaths in the categories used as the baselines for internal rate-based RRs. The NCI findings also did not adequately account for the

duration of time subjects spent in the highest peak category (or for AIE, duration of exposure) or the time since their first peak exposure (or for AIE, time since first exposure). Our finding that NCI's suggestion of a causal association was not robust with respect to alternative categorizations of formaldehyde exposure and methods of data analysis cast considerable additional uncertainty regarding the validity of this suggested association (Marsh and Youk, 2004).

NCI Findings for Nasopharyngeal Cancer

In the 2004 NCI cohort study report (Hauptmann et al., 2004), the authors suggested a possible causal association between formaldehyde exposure and NPC. As for leukemia, NCI based these conclusions exclusively on internal mortality rate comparisons and were observed for only two of four formaldehyde exposure metrics considered, in this case, highest peak formaldehyde exposure and cumulative formaldehyde exposure. NCI's internal analyses showed no statistically significant exposure-response relationship of the risk of NPC with average intensity of formaldehyde exposure or with duration of formaldehyde exposure. The authors of the NCI report concluded, *"In summary, analysis of this cohort of workers in the formaldehyde industry, which included additional years of follow-up, supports a possible causal association with mortality from cancer of the nasopharynx and possibly other upper respiratory tract sites." (Hauptmann et al., 2004, page 1129)*.

University of Pittsburgh Reanalyses of NCI Nasopharyngeal Cancer Data

In 2005, we performed an extensive reanalysis of the detailed NCI cohort data file to determine whether the NCI's suggestion of a causal association between formaldehyde exposure and mortality from NPC was robust with respect to alternative characterizations and categorizations of formaldehyde exposure and to alternative methods of data analysis (Marsh and Youk, 2005). Using the original cohort data provided by NCI, we computed U.S. and local county (regional) rate-based standardized mortality ratios (SMRs) and internal cohort rate-based relative risks (RR) by categories of four formaldehyde exposure metrics (highest peak, average intensity, cumulative, and duration of exposure), using both NCI categories and an alternative categorization based on tertiles of all NPC deaths among exposed subjects. We computed SMRs and RRs for each of 10 study plants and by plant group (Plant 1, n=4261 vs. Plants 2–10 n=21,358).

We found that six of 10 NPC deaths observed in the NCI study occurred in only one plant (Plant 1) and the remaining four cases occurred randomly and individually in four of the other nine plants studied. A large, statistically significant, regional rate-based NPC SMR of 10.32 (95% CI=3.79–22.47) among formaldehyde-exposed workers in Plant 1 contrasted sharply with a 35% deficit in NPC deaths (SMR=0.65, 95% CI=.08–2.33) among exposed workers in Plants 2–10 combined.

We also found that the statistically significant exposure–response relationship with formaldehyde and NPC reported in the NCI study for highest peak exposure was driven entirely by a large, statistically significant excess NPC risk in Plant 1 for the highest peak exposure category (4+ ppm). For the remaining nine plants, RRs for all non-baseline highest peak exposure categories were less than 1.0, and we observed no evidence of an exposure–response relationship. Most of the observed NPC excesses for the non-baseline categories of the other exposure metrics (average intensity, cumulative, and duration of formaldehyde exposure) were concentrated in Plant 1, and by contrast to the NCI findings, none of the corresponding exposure–response relationships was statistically significant. This distinct contrast in the findings for NPC in Plant 1 compared with the remaining nine plants was not recognized in the NCI report (Hauptmann, et al., 2004).

We found that our reanalysis of the NCI cohort data provided little evidence to support NCI's suggestion of a causal association between formaldehyde exposure and mortality from NPC. We concluded that our findings cast considerable additional uncertainty regarding the validity of NCI's suggested causal association with formaldehyde and NPC (Marsh and Youk, 2005).

In 2007, in collaboration with our German colleague, Dr. Peter Morfeld (from the Institute for Occupational and Social Medicine, Cologne University Medical School, and the German Institute for Occupational Sciences of RAG Aktiengesellschaft in Dortmund, Germany), we performed two additional types of re-analyses of the NCI cohort data with focus on the NCI metric, "highest peak exposure" and NPC mortality (Marsh et al., 2007a). These rigorous statistical analyses were aimed at: (1) investigating whether the model specification chosen by Hauptmann et al. (2004) was appropriate (interaction assessment) and (2) exploring the degree of instability of the risk estimates for NPC in relation to highest peak exposure (sensitivity analysis).

We found that Hauptmann et al. (2004) failed to account for an important interaction structure between plant group and the exposure variable that prohibited a generalization of formaldehyde effects within the NCI cohort and, in particular, beyond the NCI cohort. In addition, our sensitivity analysis demonstrated considerable uncertainties in the risk estimates due to the small numbers of observed NPC deaths and pointed convincingly to instability problems particularly related to Plant 1. We found that even a simple sensitivity model taking only one additional death into account produced a variation of the risk estimates beyond the instability conveyed by standard confidence intervals.

We concluded that the results of our modeling-based reanalysis of the NCI study did not support NCI's suggestion of a causal association with formaldehyde exposure and NPC. Based on these findings we also concluded that the decision by the IARC working group to reclassify formaldehyde as a Group 1 substance in 2004 was clearly premature considering: (1) the missing evidence of an NPC excess from the large British (Coggan et al., 2003) and NIOSH (Pinkerton et al., 2004) cohort studies; (2) the absence of an association with formaldehyde and NPC, and the identification of an external exposure that may explain the NPC excess in the independent and expanded University of Pittsburgh study of Plant 1 (described below); and (3) the mis-specified and non-robust internal analysis of the NCI cohort study that failed to recognize the anomalous Plant 1 findings for NPC, brought to light in our reanalyses of the NCI cohort study data (Marsh and Youk, 2005, Marsh et al., 2007a).

The University of Pittsburgh's Independent Study of NCI's Plant 1

Plant 1 in the NCI study has been studied independently at the University of Pittsburgh by Marsh et al. (Marsh et al.; 1994; 1996; 2002; 2007b) to investigate further the possibility that the large, anomalous nasopharyngeal cancer (NPC) mortality excess in the NCI cohort study of formaldehyde-exposed workers may be related to occupational factors external to the study plant. We expanded the original NCI cohort definition to include 7345 workers employed at a plastics-producing plant between 1941 and 1984 (the NCI study was limited to workers hired before 1966). We determined vital status for 98% of the cohort and cause of death for 95% of 2872 identified deaths. Independently reconstructed worker exposures to formaldehyde were used to compute unlagged and lagged exposure measures, including duration or exposure, average intensity of exposure and cumulative exposure.

We computed standardized mortality ratios (SMRs) based on US and local county rates. In a nested case–control study that collected information on subjects' lifetime smoking histories and prior employment histories, we evaluated mortality risks from NPC and from all other pharyngeal cancers combined (AOPC) in relation to formaldehyde exposure while accounting for potential confounding or effect modification by smoking or external (non-Wallingford) employment. Job applications, Connecticut commercial city directories and a previous survey were also used to assign subjects to three external job groups.

Our study found no new deaths from NPC and one additional AOPC death (pharynx unspecified) yielding, respectively, SMRs of 4.43 (7 deaths, 95% CI = 1.78–9.13) and 1.71 (16 deaths, 95% CI = 1.01–2.72). Five of seven NPC cases had worked before or after employment in Plant 1 in silver smithing (including brass plating and other jobs related to silver or brass) or other metal work (including steel working and welding), and this type of work was relatively rare in the remaining study population (OR = 14.41, 95% CI = .08–82.1). For AOPC, we found a moderate increase in risk for other metal work (OR = 1.40, 95% CI = .31–5.1). Interaction models suggested that NPC and AOPC risks were not elevated in subjects exposed only to formaldehyde.

We concluded that the results of our independent nested case–control study suggested that the large NPC mortality excess in Plant 1 cohort may not be due to formaldehyde exposure, but rather reflects the influence of external employment in the ferrous and nonferrous metal industries of the local area that entailed possible exposures to several suspected risk factors for upper respiratory system cancer (e.g., sulfuric acid mists, mineral acid, metal dusts and heat). Our findings may also help to explain why the associations with formaldehyde and nasopharyngeal cancer reported in the 1994 update of the 10-plant NCI formaldehyde cohort study were unique to Plant 1 (Marsh et al., 2007b).

IARC's 2004 Reclassification of Formaldehyde

In 2004, IARC relied heavily upon the 2003 and 2004 NCI reports when making their decision to reclassify formaldehyde as a Group 1 (known human carcinogen) (IARC, 2006). IARC made their decision based on "sufficient" evidence for a causal association between NPC and exposure to formaldehyde, and "strong but not sufficient" evidence for a causal association between leukemia and exposure to formaldehyde. Unfortunately, at the time of their 2004 decision to

reclassify formaldehyde as a known human carcinogen, IARC did not have available the 2007 results of our latest update of Plant 1 that included six of 10 observed NPC deaths in the NCI study. As noted above, our independent and expanded cohort study of NCI's Plant 1 found little evidence that that the anomalous finding for NPC in Plant 1 was associated with formaldehyde exposure, but is more likely related to previous work in the extensive, local metal industry (Marsh et al., 2007b).

In 2004, IARC also did not have available the results of our later reanalyses of the NCI cohort that cast considerable doubt on regarding the validity of the suggested associations with formaldehyde and leukemia and NPC (Marsh and Youk, 2004; 2005; Marsh et al., 2007a). Finally in 2004, neither IARC nor NCI was aware of the fact (later identified and reported by Beane Freeman et al., 2009b) that 1,006 deaths were missing from the 1994 follow-up of the NCI cohort and that proportionally more of these missing deaths occurred among subjects in the unexposed and low exposed subgroups that served as the baseline or comparison groups in the internal relative risk comparisons (more details about this omission are described in a later section).

The 2004 Follow-up of the NCI Cohort Study

In 2009, NCI published a 2004 follow-up of the formaldehyde worker cohort that focused again on lymphohematopoietic malignancies (Beane Freeman, et al., 2009a).[1] This update added 5465 deaths to the NCI cohort including 178 deaths from lymphohematopoietic malignancies. The epidemiological and statistical methods used by NCI in the 2004 update were, for the most part, identical to those reported in NCI's previous mortality (through 1994) update (Hauptmann et al., 2003). Thus, many of the criticisms concerning NCI's methodology and interpretation of findings that we noted in our 2004 reanalysis (Marsh and Youk, 2003) also apply to the current update, in particular, reliance on internal mortality comparisons and incomplete or inappropriate analyses of highest peak formaldehyde exposure.

[1] NCI is currently working on an analysis of data from the 2004 follow-up of the formaldehyde worker cohort that will focus on solid tumors, in particular, nasopharyngeal cancer (NPC). This update on the NPC mortality experience of the cohort will help to inform the state of the science on the potential human carcinogenicity of formaldehyde.

New methods used by NCI in the 2004 follow-up included the use of a fifth formaldehyde exposure metric, "total number of peak exposures above 4.0 ppm", although no biological or other justification is given by the authors for the use of this metric. Another new method was a detailed analysis of mortality risks by annual follow- up increments and a sensitivity analysis to assess the effect of assuming zero formaldehyde exposure after 1980 (as in the 1994 follow-up, NCI did not develop estimates of worker exposure to formaldehyde after 1980). As in the 1994 NCI update (Hauptmann et al., 2003), the methodology section of the current report neither adequately describes nor justifies the use of the highest peak formaldehyde exposure metric (or the new "total number of peaks above 4.0 ppm" metric) on biological and/or statistical grounds. This is a major methodological shortcoming, as the conclusions of the previous and current NCI updates were driven heavily by the findings for the highest peak formaldehyde exposure metric.

Compared with the 1994 follow-up, the 2004 follow-up revealed less evidence of an association between formaldehyde exposure and mortality from lymphohematopoietic malignancies, especially for the subcategories of *a priori* interest, all leukemia and myeloid leukemia. This evidence for weakened associations included substantially attenuated exposure-response relationships for all lymphohematopoietic malignancies, all leukemias and myeloid leukemia, the disappearance of the statistically significant exposure-response relationship for all lymphohematopoietic malignancies based on average intensity of formaldehyde exposure and for myeloid leukemia based on the highest peak metric (reported in 1994 update), the absence of an association for any of the categories examined for the new total number of peaks above 4.0 ppm metric and the reduction in risks for all leukemia and myeloid leukemia following extended observation time.

Despite the weakened associations for lymphohematopoietic malignancies clearly evident in the data presented in the 2009 report, the NCI investigators again suggest a possible causal association with formaldehyde exposure. In particular, the NCI authors concluded for myeloid leukemia, *"In the current follow-up, the overall risk of myeloid leukemia has declined from our previous report, but remains somewhat elevated. Although that time trend may suggest that the previous excess risk estimates were due to chance, the pattern is consistent with a possible causal association, with the largest risks occurring closer in time to relevant exposures."(Beane Freeman, et al., 2009a, page 760).*

Corrected Data for the NCI Cohort Study (1994 Follow-up)

In the most recent 2004 follow-up of the NCI study, the authors noted that NCI had missed 1,006 deaths among cohort members in the previous 1994 follow-up (Beane Freeman et al., 2009a). This led to the 2009 online publication by NCI (Beane Freeman et al., 2009b) of four corrected tables from the earlier 2003 and 2004 publications (Hauptmann et al., 2003; 2004). A key change in the original findings for leukemia (Hauptmann et al., 2003) was that NCI had missed proportionally deaths more among the unexposed and low exposed groups that served as the baseline or comparison groups in the internal relative risk comparisons. This new finding is consistent with findings of the Marsh and Youk (2004) reanalysis, which showed that the exposure-response association for leukemia originally reported by Hauptmann et al. (2003) was due largely to a deficit in deaths among the low or unexposed subgroups.

Although the corrected NCI study tables do not show results separately for NPC, the corrected results for the category "all solid tumors" suggest that the original NCI results for NPC may also be incorrect. This observation coupled with the finding of Marsh et al. (2007) that only one additional NPC death may have important influence on the exposure-response for NPC, suggest that the original NCI exposure-response data for NPC should not be accepted as valid scientific evidence for evaluating the potential human carcinogenicity of formaldehyde.

Summary of Comments and Conclusions

1. The Marsh and Youk (2004) reanalysis of the 1994 follow-up of the NCI cohort study of formaldehyde-exposed workers (Hauptmann et al., 2003) provided little evidence to support NCI's suggestion of a causal association between formaldehyde exposure and mortality from leukemia (all types combined) and myeloid leukemia.

2. The Marsh and Youk (2005) and Marsh et al. (2007a) reanalyses of the 1994 follow-up of the NCI cohort study of formaldehyde-exposed workers (Hauptmann et al., 2004) provided little evidence to support NCI's suggestion of a causal association between formaldehyde exposure and nasopharyngeal cancer (NPC). NCI's suggestion of a possible causal association for NPC was driven heavily by anomalous findings in one study plant (Plant 1) that were not recognized by the NCI investigators.

3. The results of the independent University of Pittsburgh cohort and nested case–control studies of workers in NCI's study Plant 1 suggested that the large NPC mortality excess in Plant 1 may not be due to formaldehyde exposure, but rather reflects the influence of external employment in the ferrous and nonferrous metal industries of the local area that entailed possible exposures to several suspected risk factors for upper respiratory system cancer (e.g., sulfuric acid mists, mineral acid, metal dusts and heat) (Marsh et al., 2007b).

4. The 1994 follow-up of the NCI cohort study of formaldehyde-exposed workers (Hauptmann et al., 2003; 2004) yielded questionable, non-robust and, in some cases, incorrect results for lymphohematopoietic malignancies and NPC that were used by the International Agency for Research on Cancer (IARC) to make inappropriate and misleading decisions regarding human cancer risk from formaldehyde (IARC 2006).

5. The 2004 decision by IARC to reclassify formaldehyde as a Group 1 substance was clearly premature considering: (1) the missing evidence of an NPC excess from the large British (Coggan et al., 2003) and NIOSH (Pinkerton et al., 2004) cohort studies; (2) the failure of the NCI to recognize that their suggestion of a possible causal association with NPC and formaldehyde was driven heavily by anomalous findings from one study plant (Plant 1) (Marsh and Youk, 2005, Marsh et al., 2007a); (3) the incompleteness and inaccurateness of data from the 1994 follow-up of the NCI cohort revealed in corrected tables recently published by NCI (Beane Freeman, 2009b); and (4) the absence of an association with formaldehyde and NPC in the independent and expanded University of Pittsburgh study and the new evidence from this study that the large NPC excess in Plant 1 may reflect the influence of external employment in the ferrous and nonferrous metal industries of the local area that entailed possible exposures to several suspected risk factors for upper respiratory system cancer (Marsh et al., 2007b).

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