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February 8, 2010

Dr. Ruth Lunn
Director
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Re: National Toxicology Program (NTP); Report on Carcinogens (RoC) Center: Request for Public Comments on the RoC Expert Panel's Recommendation on Listing Status for Formaldehyde and the Scientific Justification for the Recommendation, 74 Fed. Reg. 67883 (December 21, 2009)

Dear Dr. Lunn:

Enclosed are the comments of Georgia-Pacific, LLC ("GP") on the Recommendation from the Expert Panel Report (Part B) on Formaldehyde. GP appreciates the opportunity to comment on this important report.

GP is one of the world's leading manufacturers and marketers of building products, tissue, packaging, paper, market pulp, cellulose, and related chemicals with about 165 manufacturing facilities across the United States. GP (through its operating/manufacturing subsidiaries) has a significant interest in the Expert Panel Report being completed based on objective and sound scientific reasoning.

GP strongly disagrees with the Panel's conclusion to list formaldehyde, a natural component of every cell in the body, as a human carcinogen. GP urges the National Toxicology Program to consider these comments and update the Expert Panel Report accordingly, reflecting that formaldehyde should keep its current listing as Reasonably Anticipated to be a Human Carcinogen. GP generally endorses the comments being submitted by the Formaldehyde Council, Inc., in which GP is a member.

If you have any questions or need additional information about these comments, please feel free to contact Stewart Holm (404-652-4275) or me (404-652-4776).

Sincerely,

[Redacted]

Traylor Champion
Vice President, Environmental Affairs

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Georgia-Pacific

COMMENTS ON THE RECOMMENDATION FROM THE EXPERT PANEL REPORT (PART B) ON FORMALDEHYDE

74 *Fed. Reg.* 67883 (December 21, 2009)

I. The Weight of the Evidence Does Not Support the Causal Association Between Formaldehyde Exposure and Leukemia Including Myeloid Leukemia

According to the Expert Panel Report, four studies played a "key role" in its evaluation of the association between formaldehyde and leukemia, and based on these four studies, the Panel concluded that the "strongest evidence for an association between formaldehyde exposure and leukemia is for myeloid leukemia." The four studies referenced are Coggon *et al.* (2003), Pinkerton *et al.* (2004), Beane Freeman *et al.* (2009), and Hauptmann *et al.* (2009). These four studies, if key to the panel's assessment, should be required to show a significant excess of myeloid leukemia with a positive dose-response relationship where chance, bias, and confounding are unlikely to explain any observed excess in this cancer. These four studies are clearly the most informative human studies related to formaldehyde and worker exposure. Unfortunately, there is a striking disconnect between the Expert Panel's conclusions about these studies and what is actually reported by the authors.

- **Coggin et al. (2003).** This study reported no statistically significant excess in leukemia. An important feature of this study is that it likely involved the highest exposures to formaldehyde of the four key studies cited. Because myeloid leukemia was not separately reported this study offers no support for the conclusion of the expert panel that this endpoint is known to be a consequence of formaldehyde exposure.

- **Pinkerton et al. (2004).** As reported by Pinkerton et al. (2004), the SMR for myeloid leukemia was a non-statistically significant 1.44 (95% CI 0.80 to 2.37). A significant association for myeloid leukemia after more than 20 years of exposure was reported (Table 4), but this appears to be an error, i.e., since the text clearly shows that neither of the SMRs for 10 years since first exposure (SMR=1.91, 95% CI 0.62-4.45) nor 20 years since first exposure (SMR=1.84, 95% CI 0.84-3.49) were statistically significant.

- **Beane Freeman *et al.* (2009).** In this study, there was no statistically significant increase associated with average intensity or cumulative exposure to formaldehyde. Leukemia was significantly elevated for the peak exposure metric, however, myeloid leukemia was not significantly elevated based on peak exposure and the exposure-response trend was also not significant (P_{trend} = .13 and .07 compared to exposed and unexposed workers,

respectively). In other words, there was no positive dose-response relationship for this endpoint.

- **Hauptmann et al. (2009).** This study reported a positive association between embalming (ever worked) and myeloid leukemia. The study did not find a relationship with lymphohematopoietic cancers of lymphoid origin. However, none of the exposures were actually measured, an important deficiency that could lead to a large potential bias in this study. Rather exposures were inferred based on number of embalmings performed, which was used as an exposure surrogate.

By totaling the observed and expected mortality with a statistical test from the first three studies for which data are available that allow this method to be applied a total of 152 cases were observed while 153.2 would be expected. As shown in Table 1 the observed and expected leukemia mortality data from the three major epidemiologic studies of formaldehyde-exposed workers illustrates quite clearly that there is no excess.

Table 1: Comparison of Observed and Expected Leukemia Mortality in Three Large Cohorts of Formaldehyde-Exposed workers

	25,000	116	≈ 116
	14,000	12	13.2
	11,000	24	≈ 24
	50,000	152	153.2

This simple analysis does not substitute for a meta-analysis, but it does illustrate that among some 50,000 formaldehyde industry workers examined, there is no evidence of a marked excess of leukemia in these cohorts. While this does not directly address myeloid leukemia, if there is no difference in overall leukemia mortality, there cannot be an excess in myeloid leukemia.

In addition to the cohort studies, meta-analyses have been conducted on the body of epidemiologic studies concerning the lack of an association between formaldehyde and leukemia. Only the most recent, Bachand *et al.* (2009), includes the recent NCI study update. For cohort studies, summary risk estimates (REs) ranged from 0.43 to 1.60 for leukemias, with all but one study reporting no association. For two case-control studies the RE was 0.98 (95% CI: 0.70, 1.36) for Blair *et al.* (2001) and 1.40 (CI: 0.25, 7.91) for Partanen (1993). Meta-regression showed the overall leukemia RE was 1.05 (95% CI: 0.93, 1.20). No evidence for an increase in leukemia was noted, even in the higher exposure studies.

In addition to these general observations, a more intensive review of a few of the main studies is presented below.

Beane-Freeman et al. (2009)
Beane-Freeman et al., 2009 is a follow-up to Hauptmann, 2003. The study design in Beane-Freeman in 2009 continued to use "peak" as an exposure metric. In 2004, Marsh et al. reanalyzed NCI's 2003 data, and challenged the validity of NCI's leukemia findings on grounds of biological implausibility and inadequate or questionable methods of data analysis. This analysis also described the unusual statistically significant deficits in leukemia mortality in the low exposed and unexposed groups used for internal comparisons in all of the analyses which drove the outcome for the "peak" exposure metric. NCI has stated that internal comparisons are necessary because comparisons to larger populations are confounded by the "healthy worker effect." Although the healthy worker effect is well known for non-cancer causes of death such as diseases of the respiratory system, such an effect is not found with cancer endpoints (Greenberg et al., 2001). While no one would disagree that, all other things being equal, the internal comparison is likely the best for comparison purposes this does not apply when there is a statistically significant deficit in the low and no exposed groups. In addition, consistency is important in making causality determinations. As shown in this reanalysis, mortality comparisons of formaldehyde-exposed workers with local expected rates yielded no cancer excess.

In the most recent follow-up of the NCI study it was revealed that Hauptmann (2003, 2004) had missed 1,006 deaths among cohort members in the previous 1994 follow-up, as already identified by Marsh and Youk (2004). This led to the 2009 online publication by NCI (Beane Freeman *et al.*, 2009b) of 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 more deaths among the low-exposed and unexposed subgroups that served as the baseline 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 statistically significant deficits in deaths among the low-exposed and unexposed subgroups. As shown by Marsh and Youk, the impact of the missed deaths is substantial. Indeed, the missed deaths change the significant trend reported to insignificant for the exposed workers in the original 1994 follow-up. This change in results was not adequately debated at the NTP Expert Panel meeting and appears to have been forgotten in its analysis. The resulting listing outcome, thus, may likely be based, in part, on an incomplete and flawed paper.

Hauptman et al. (2009)
Most of the studies on embalmers, pathologists, and anatomists report increased risk of leukemia. These findings have largely been attributed to either reporting bias, some exposure other than formaldehyde related to the embalming, or to infectious agents (Harrington and Shannon 1975, Walrath and Fraumeni 1983, 1984, Stroup et al. 1986, Hayes et al. 1990). Given the lack of myeloid leukemia findings in some of the industrial studies with even higher formaldehyde exposures as discussed above, it is plausible that the findings of increased myeloid leukemia risk in this study may be

due to factors other than formaldehyde, since it is well known that embalming fluids are complex mixtures including many chemicals in addition to formaldehyde. Moreover, the probability of being in contact with viruses (a possible risk factor for leukemia) associated with working with tissue cannot be ignored. Consequently, since the number of embalmings was one of the best predictors of risk of myeloid leukemia, it cannot be ruled out that that another component of the embalming fluids is related to the increased risk observed. This is particularly the case since formaldehyde exposures were never actually measured.

II. Biomarkers of Exposure/Response Are Conflicting

Zhang *et al*., 2010, showed evidence of aneuploidy in human chromosomes 7 and 8 in myeloid progenitor cells from formaldehyde-exposed workers. Although the authors themselves stated that this study must be replicated, the NTP panel appeared to have relied heavily on this paper in making its assessment. However, in assessing the relevance and strength of this study, NTP should consider that: (1) Chromosomes 7 and 8 are believed to be minimally relevant to leukemia and the number in peripheral blood lymphocytes (PBL) is not known to have any predictive value or to be evidence of toxicity, (2) there is no existing accepted diagnostic test in clinical medicine, hematology or hematopathology that can establish the presence of leukemia, or increased likelihood of the development of leukemia, by detection of monosomy 7 or trisomy 8 in cultured peripheral blood lymphocytes, and, (3) there is little evidence of chromosomes 7 and 8 being associated with leukemia. For example, in 122 AML patients in China, none had monosomy 7 and only 4 had trisomy 8. Reference: Zheng, et al. Cytometry Part B: Clinical Cytometry, 74B, pages 25-29, 2007.

In addition, the data are conflicting for hematotoxicity. This is a key issue as hematotoxicity, which is an indicator of myelotoxicity, has been associated with all known human leukemogenic chemicals and is a necessary precursor for leukemogenesis. In fact, Zhang et al. (2010) reported decreased red and white blood cell counts in the exposed individuals compared to unexposed although all were in the normal range. This finding could have been due to formaldehyde exposure, other chemical exposure, false positive statistics or other events. However, it was interpreted by Zhang as an early sign of pancytopenia as is seen in all chemically-induced leukemias. Assuming these data can be validated, the only possible way to account for this is bone marrow depression (i.e., myelotoxicity). With respect to these two issues, i.e., formaldehyde-induced pancytopenia and myelotoxicity, a recent study conducted in male F-344 rats suggest that neither is a consequence of formaldehyde exposure. In this well-controlled study, animals were exposed to formaldehyde via inhalation to concentrations of 0, 0.7, 2, 6, 10 and 15 ppm for 90 days. There were no significant effects on red or white blood cell counts and no effects on the bone marrow. This study (currently in preparation for publication) indicating a lack of either hematotoxicity or myelotoxicity calls into question the source of the reported changes as described by Zhang et al.

In contrast to the above, the vast majority of more credible data show essentially no reported hematological effects following exposure of either humans or animals to formaldehyde. This has substantial implications with respect to any hypothesized mechanism for formaldehyde-induced myeloid leukemia, since no matter how one might postulate that this occurs (e.g., formaldehyde-induced myelotoxicity or formaldehyde-induced mutations to stem cells with subsequent transport to the bone marrow), all would require pancytopenia as an early indicator of potential disease. While accidental ingestion of a large quantity of formaldehyde was reported to cause an intravascular coagulopathy (Burkhart et al., 1990), several reports of human ingestion of lower doses have not shown any effects on the blood or blood-forming organs (Eells et al. 1981, Freestone and Bentley 1989, Koppel et al. 1990). In animal studies, neither inhalation exposure (Appelman et al. 1988, Kamata et al. 1997, Kerns et al. 1983, Woustersen et al. 1987) nor oral exposure (Johannsen et al. 1986, Til et al. 1989, Tobe et al. 1989) to high doses of formaldehyde has produced any evidence of adverse hematological effects. A single study in rats exposed to massive oral doses of formaldehyde (e.g., 80 mg/kg for 4 weeks) reported minor alterations in erythrocyte count and hemoglobin values (Vargova et al. 1993). As noted in ATSDR (1999), the lack of hematopoietic toxicity in these studies is "likely related to rapid metabolism prior to the formaldehyde reaching the blood and blood-forming components (bone marrow)."

III. Animal Studies Do Not Support Biological Plausibility of Formaldehyde Causing Leukemia

A. Inhalation Exposure

There are numerous formaldehyde inhalation studies; however, these studies focused on site of contact tumors, i.e., nasal tumors were the only endpoint reviewed. Consequently, distant site tumors were not investigated. Recently, it has been reported (Andersen, pers com) that inhaling up to 15 ppm formaldehyde for 90 days has no adverse effects on red or white blood cell counts or on the bone marrow, which are essential precursors to this disease. These findings, indicating that the triggering events in the development of leukemia do not occur, are important in evaluating the biological plausibility that inhalation exposure to formaldehyde might cause leukemia.

B. Drinking Water Exposure

Tobe et al. (1989) administered formaldehyde to rats in their drinking water at concentrations of 0, 0.02, 0.10 and 0.5 % for 24 months. While numerous tissues were examined for potential adverse effects, lymphohematopoietic malignancies were not specifically mentioned. Red blood cell and white blood cell counts and hematocrit were measured on each animal at necropsy. No dose-related effects were observed for any of these endpoints. Importantly, the fact that the white blood cell count was unaffected by the

large doses used has implications for discussion of biological plausibility for formaldehyde-induced leukemia.

In addition, Til et al. (1989) conducted another study in which formaldehyde was administered to rats in their drinking water at doses of 5, 25, 125 mg/kg for two years. Blood samples were collected from 10 rats/sex/dose group at 26 and 103 weeks and examined for the same endpoints as above. While histopathology examinations did not include bone marrow, axillary lymph nodes were examined. After two years of exposure there were no differences between dose groups in any hematological parameters, no dose-related lymphoma in axillary lymph nodes, and no evidence of myeloid leukemia in blood cells. This study was negative for any tumor endpoint after oral formaldehyde administration.

Of the many carcinogenicity studies on formaldehyde, the only one that has reported a carcinogenic effect at a site distant from the point of administration (i.e., nasal passages or gastric mucosa) was by Soffritti et al. (1989). Because of the numerous questions concerning the conduct of this study, it is difficult to judge the findings in context with other data. In reviewing the results of Soffritti et al. (1989), ATSDR (1999) expressed skepticism: "Another limitation to the strength of the evidence for formaldehyde-induced leukemia is the lack of a consistent dose-response relationship in the Soffritti et al. study. . .The second part of the Soffritti et al. (1989) study found no statistically increased incidence of leukemia in groups of breeding pairs of rats or their offspring exposed for life to the higher dose level of 313 mg/kg/day. A further limitation is the absence of corroborating evidence for effects at sites distant from portals-of-entry in the other drinking water rat studies, and in inhalation-exposure animal studies." The Cancer Assessment Committee of the Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (FDA), also reviewed the study of Soffritti et al. (1989), concluding that the data reported were "unreliable" due to "a lack of critical detail. . .questionable histopathological conclusions, and the use of unusual nomenclature to describe the tumors." Consequently, the FDA "determined that there is no basis to conclude that formaldehyde is a carcinogen when ingested" (U.S. FDA, 1998).

IV. Conclusion

For the reasons presented in these comments, the carcinogen listing status of formaldehyde should remain unchanged. Given the documented extent to which chance, bias, and confounding are likely to explain the observed excess for leukemia, including myeloid leukemia, there is simply no basis for concluding that formaldehyde causes this disease.

REFERENCES

References not cited in the background document are listed below:

Melvin E. Andersen, PhD. Pers com. February 3, 2010

Greenberg, R.S., Mandel, J.S., Pastides, H., Britton, N.L., Rudenko, L., and Starr, T.B. A meta-Analysis of Cohort Studies Describing Mortality and Cancer Incidence among Chemical Workers in the United States and Western Europe. Epidemiology. Vol. 12, No. 6. November 2001