Comments on Formaldehyde Expert Panel Report – Part B
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I have read the Expert Panels Report and offer the following comments.

P2, para 6: Accompanying these comments are two recently accepted papers that should be part of the record of the NTP-ROC Formaldehyde Report and Panel reports. The first of these papers is in press in the *Journal of the American Chemical Society*. This manuscript provides a detailed characterization of the reactions of amino acids and deoxynucleosides and their oligomers, which has direct relevance to formaldehyde's DNA adducts. The second manuscript provides the only chemical-specific data on the formation and distribution of formaldehyde DNA adducts following inhalation exposure. This information was presented at the NTP meeting on November 2, 2009, so the Panel is aware of it. It is now accepted for publication in *Toxicological Sciences*. The information in this paper directly addresses the issue of toxic effects at sites distal from the point of contact and provides highly specific and sensitive data that demonstrates that inhaled formaldehyde does not reach distant tissues including bone marrow, white blood cells, spleen, thymus, liver and even lung of rats exposed to 10 ppm [$^{13}CD_2$]-formaldehyde. The methods allow precise quantitation of both endogenous and inhalation-specific DNA adducts of formaldehyde. We demonstrated that N^2-hydroxymethyl-dG monoadducts and dG-dG cross-links form in nasal respiratory epithelial DNA, the site of the squamous cell carcinomas, but not in tissues remote to the portal of entry. No N^6-HO$^{13}CD_2$-dA adducts were detected in nasal DNA, but high amounts of endogenous formaldehyde dG and dA monoadducts were present in all tissues examined. In fact, steady-state concentrations of endogenous formaldehyde adducts were 2.5 – 3 times greater than the inhalation-specific N^2-HO$^{13}CD_2$-dG adducts that are formed from 5 days exposure to 10 ppm formaldehyde. None of the other data in the published literature has chemical-specific data. Thus, it provides compelling data that should bring the Panel to the opposite conclusion reached in this paragraph. Furthermore, the NTP-ROC report needs to be amended to bring this evidence forward.

P 4-24, Nasopharyngeal, sinonasal cancer and leukemia: This section of the Panel's report does not give adequate weight to several major issues. I have followed the UK cohort ever since we discovered that formaldehyde was carcinogenic. At that time Dr. Acheson was the epidemiologist evaluating worker exposure. He met with us at several meetings and frequently brought forward the high concentrations that workers were exposed to (up to 10 ppm). Coggon has since been the epidemiologist for this study. This large cohort of over 14,000 workers with high exposure did not find any increase in nasopharyngeal or sinonasal cancer, yet this is not discussed in the Panel's report. Likewise, Coggon has a 0.71 relative risk for leukemia in the highly exposed workers. While it is listed in Table 3, it is not discussed. Similarly, the data from Marsh relating to the fact that 5/9 NPC in the NCI study occurred in Plant 1 and that many of these individuals had also been employed in metal work, an industry with a known relationship to human NPC, was not discussed adequately. It is imperative that supportive and negative studies and confounders be treated in a more open process for the Panel's report to be credible.

P 26, para 1: The report has correctly been critical of the Soffritti rat study. The authors of this study were petitioned by the NTP, FDA and EPA to allow this study to undergo a peer review using a standard Pathology Working Group procedure, but were denied access to the histopathology slides. Recently, a paper raises questions on the lymphomas diagnosed in the lung possibly being chronic mycoplasma infections, not lymphoma (Schoeb et al, *Toxicologic Pathology* 46: 952-959, 2009).

P 26, para 2: The paper by Pala et al, 2008, does not provide direct evidence that inhaled formaldehyde enters the blood. It cannot differentiate endogenous albumin adducts from exogenous adducts. Furthermore, it did not control for diet or drugs, which can be demethylated in the liver, the site of albumin formation. The Panel did not report that no effects were seen for micronuclei, chromosome aberrations or SCEs. Thus, the panel appears to be being selective in reporting results that they thought would support inhaled formaldehyde as a possible leukemogen. The Wang, 2009, paper on smokers and formaldehyde adducts is consistent with formaldehyde arising from metabolism of nitrosamines and NNK, not inhalation. Inhaled formaldehyde does not cause dA mono adducts. Shaham's data are not chemical specific and it does not appear to have been done in a blinded manner. Finally, in our Toxicological Sciences paper, we demonstrated that the transport of inhaled formaldehyde as methanediol, S-hydroxymethylglutathiuone, or the acetal to distant sites does not occur.

P 27, para 2: The Zhang et al, 2010, paper does not demonstrate that aneuploidy was present in chromosomes 7 and 8 of exposed workers. These changes could also have been formed during the *in vitro* culture of the CFU-GM cells.

P 28, para 1: It should be noted that carcinogenicity in rats exposed to inhaled formaldehyde has a highly non-linear exposure response that correlates very well with cell proliferation. Based on the data from the attached Toxicological Sciences paper, one would get more mutations from the endogenous formaldehyde adducts than from the inhalation specific adducts. If one models the number of inhalation specific adducts at low concentrations, such as 0.1 ppm, only 1/1000 of the adducts would come from the exposure. The reason nasal carcinomas are so rare in rats is due to the low rate of cell proliferation at non-cytotoxic exposures.

P 28, para 2: Formaldehyde has not been shown to damage liver, testes and lymphocytes following inhalation in any consistent manner. In fact, the data suggest the opposite. The Pala et al, 2009, paper actually showed the opposite effect for lymphocytes. In contrast, the attached Toxicological Sciences paper presents compelling data that damage distant to the portal of entry does not occur and it seriously detracts from the strength of evidence that formaldehyde causes leukemia. This new data needs to be incorporated into the NTP-ROC Report on Formaldehyde and the Formaldehyde Expert Panel's Report.