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Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
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Building 4401
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Via Email: jameson@niehs.nih.gov

*RE: COMMENTS ON FORMALDEHYDE NOMINATION TO REPORT ON CARCINOGENS,
FEDERAL REGISTER NOTICE, TUESDAY, OCTOBER 18, 2005*

Dear Dr. Jameson:

The Methanol Institute (MI) is submitting comments concerning the proposed reclassification by the National Toxicology Program (NTP) of formaldehyde as a human carcinogen through the Report on Carcinogens. The Methanol Institute serves as the trade association for the global methanol industry. Formaldehyde is a metabolite of methanol and, therefore, MI is concerned by the proposed action of NTP. In 2005, the production of formaldehyde will consume approximately 2,500,000 metric tons of methanol (or over 800 million gallons), representing the largest market demand for methanol in the United States. Formaldehyde is one of the essential chemical building blocks of the U.S. economy, essential to the operations of nearly 50,000 facilities in 17 major industries (Formaldehyde Council, 2005).

The NTP reclassification is based on the International Agency for Research on Cancer's (IARC) reclassification of formaldehyde, which we believe is incorrect. The IARC classification is based on a review by a panel of experts (Cogliano et al 2005). The panel is supposed to use only published peer-reviewed data, but in the IRAC review on formaldehyde some non-peer reviewed data was used.

In addition, at least one peer reviewed paper has been published since the IARC meeting that raises serious questions about IARC conclusions. MI strongly recommends that the NTP carefully review all the information available – *and critical information soon to be available* – before reclassifying formaldehyde.

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To be classified as a human carcinogen by NTP, epidemiological data and/or strong mechanism data usually must be provided to support the classification. Formaldehyde had been classified by NTP as “reasonably anticipated” to be human carcinogen based on animal data demonstrating nasal cancer in rats exposed to formaldehyde by inhalation, as well as mechanistic data suggesting a possible potential to cause cancer in humans (Feron et al 1988, Kerns et al 1983, Kamata et al 1997). A *causal relationship* of exposure to formaldehyde and cancer in humans should be *clearly demonstrated* for NTP to reclassify formaldehyde as a human carcinogen.

There may be 50-plus epidemiological studies relating to formaldehyde reported in the literature. In some epidemiological studies different types of cancer have reported increased rates. No consistent pattern between studies has been seen to suggest that these are anything more than random increases due to chance, and not as a result of exposure to formaldehyde.

The key new data considered by IARC was an update of an epidemiological study of the earlier NCI study of formaldehyde workers (Blair et al 1987). The earlier study of the same population by NCI did not result in a demonstrated causal relationship between formaldehyde and cancer in humans (Blair et al 1987). The updated NCI study (Hauptmann et al 2003) concluded that there was an association of formaldehyde with leukemia. This response was not reported in a similar large industrial worker study in the United Kingdom (Coggon et al 2003).

There is extensive information on formaldehyde metabolism in animals and humans. Given the lack of effect on formaldehyde blood levels during exposure and the fact that formaldehyde is a normal metabolite, it does not seem to be biologically plausible that formaldehyde could cause leukemia (Heck et al 1985, Heck et al 2004, Casanova et al 1988, Casanova et al 2004, Cole et al 2004).

None of the several inhalation studies of formaldehyde in animals have reported an increase in leukemia (Albert et al 1982, Kerns 1983, Kamata et al 1997). Tumors were reported in the nasal cavity (site of contact) but not distant sites (Feron et al 1988, Heck et al 2004). This strongly suggests formaldehyde has no systemic effect.

There have been several oral studies of formaldehyde (Takahashi et al 1986, Til et al 1989, Soffritti et al 1989). An increase in leukemia was reported in one oral study published in a peer-reviewed journal; but the incidence rate was the same as the historical control values for that lab raising valid questions about the authors conclusions (Soffritti et al 1989). In a later report (13 years) of the same study (republished in a non-peer journal - Soffritti et al 2002), the reported incidence rate of leukemia was somehow increased in the treated animals (reviewed and used by IARC panel). This is not good science. Which report of the same research is to be believed? This is especially troubling when one considers the other oral studies of formaldehyde

that did not report leukemia as a treatment related finding (Takahashi et al 1986, Til et al 1989). Given the extensive information on formaldehyde metabolism and toxokinetics in animals, it does not seem to be biological plausible that formaldehyde could cause leukemia. Formaldehyde is a normal metabolite in both animals and humans (Heck et al 1985, Heck et al 2004, Casanova et al 1988, Casanova et al 2004, Cole et al 2004).

The IARC panel reported strong, *but not sufficient evidence* of a causal association between leukemia and formaldehyde (likely do to the extensive information on formaldehyde metabolism and lack of biological plausibility).

The other reported increase in cancer in the updated NCI study was a treatment related increase in nasopharyngeal cancer (NPC) related to peak and cumulative formaldehyde exposure in industrial workers (Hauptmann et al 2004). The majority of NPCs reported were found in one plant out of the 10 formaldehyde plants studied (Hauptmann et al 2004). The increased NPC rate in this one plant has been identified by several other authors (Blair et al 1987, Collins et al 1997, Marsh et al 2002, 2004, 2005). In one other limited study, NPC increase has also been report (Hayes et al 1990). A treatment related NPC response has not been reported in another larger worker study in the U.K. (Coggon et al 2003). Other cohort studies (Pinkerton et al.2004, Walrath and Fraumeni 1983) also report fewer case of NPC than expected.

Based on this data, the IARC panel concluded that the Hauptmann et al 2004 study provided sufficient epidemiological evidence that formaldehyde causes NPC in humans.

In a paper published **after the IARC meeting**, by Marsh and Youk (2005), from the University of Pittsburgh, a more detailed evaluation of the NPC seen in the updated NCI study was conducted (NCI supplied data to Dr. Marsh). Marsh pointed out that in 9 plants (80% of the cohort) only four NPCs were reported (1 or 0 per plant), which results in a NPC rate that is the same or lower than the general population (35% deficit when median duration and cumulative formaldehyde exposure was greater than plant one). Marsh reports six NPCs in the remaining one plant, a rate that is clearly elevated compared to the normal population (10 fold increased risk). According to Marsh the cause of the increase in this one plant has not been identified, and there is no reason to conclude a causal relationship to formaldehyde exposure. Three other cohort studies of industrial workers did not report any increase in formaldehyde exposure related NPC (Coggon et al 2003, Pinkerton et al 2004, Marsh et al.2004, Collins et al 1997).

Marsh's reanalysis concluded that the data does not support a causal relationship between formaldehyde and NPC. Something is different in this exposed population in this one plant. This more detail examination strongly suggests that formaldehyde is not the causative agent of NPC in plant one (Marsh and Youk 2005). As a result of this work, the *NCI is now updating the original study* adding an additional eight years of data to help clarify a number of inconsistencies. This update is expected to provide a more robust examination of the cohort study to permit a more balanced and scientific evaluation of the data. Recognizing the value of

the NCI effort to update this critical study, the U.S. Environmental Protection Agency has agreed to include this data in its health assessment of formaldehyde under the Integrated Risk Information System, effectively suspending any final report pending completion of the NCI update.

We believe that the data available on formaldehyde does not support the reclassification of formaldehyde as a human carcinogen. The IARC panel conclusion is based on NPC in the NCI study. The NPC rate is elevated based on data from one plant that is clearly different from the other formaldehyde plants in the NCI study. If the one plant is excluded from the data from the other nine plants in the NCI study, the NPC rate is not elevated and is in agreement with the other large worker studies (Coggon et.al. 2003, Pinkerton et al. 2004). We respectfully encourage the NTP to follow the example of the EPA, and withhold any final determination on the carcinogenicity of formaldehyde pending the updated NCI study.

The Methanol Institute appreciates this opportunity to comment on the nomination of formaldehyde to the Report on Carcinogens. Our comments were prepared with assistance from our consulting toxicologist Dr. John Clary of Bio Risk, an internationally recognized expert on the health effects of chemicals.

Sincerely,
[Redacted]

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