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Via Electronic Mail

Dr. Ruth Lunn
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RE: Comments on the Recommendation from the Expert Panel Report (Part B) on Formaldehyde, 74 Fed. Reg. 67,883 (December 21, 2009)

Dear Dr. Lunn:

I hereby submit comments to the National Toxicology Program's (NTP) Report on Carcinogens (RoC) Center on the recommendation and justification from the Expert Panel on the listing status of formaldehyde as *known to be a human carcinogen* in the 12th RoC.[1]

The focus of my comments is the blatant and unsubstantiated omission in the Expert Panel Report of several of my recent peer-reviewed publications dealing with our reanalyses of the National Cancer Institute (NCI) cohort study of formaldehyde-exposed workers (Marsh and Youk, 2004; Marsh *et al.*, 2007a) recently reported by Hauptmann *et al.* (2003; 2004) and Beane Freeman *et al.* (2009a;b) and our independent and expanded historical cohort study of one of the 10 plants included in the NCI cohort study (referred to as NCI's Plant No. 1) (Marsh *et al.*, 1994; 1996; 2002; 2007b).

These omissions of our extensive reanalyses and independent study are especially troublesome considering that I extensively discussed and referenced these in both my October 26, 2009 written comments on the NTP Draft Background Document for Formaldehyde[2] and my oral

[1] Formaldehyde Expert Panel Report, Part B – Recommendation for Listing Status for Formaldehyde and Scientific Justification for the Recommendation, available at http://ntp.niehs.nih.gov/?objectid=DFAF3D96-F1F6-975E-70E9156852E58764&#20091102 (hereinafter referred to as "Expert Panel Report").

[2] Comments on the National Toxicology Program Draft Background Document for Formaldehyde, Gary M. Marsh, Ph.D., October 26, 2009

comments presented at the NTP Expert Panel Meeting on November 2, 2009. From all our peer-reviewed publications, the Expert Panel Report *cited only one* - our renalysis of nasopharyngeal cancer (NPC) mortality in the NCI formaldehyde worker cohort study (Marsh *et al.*, 2005), and this citation was neither accurately represented nor fully described. We also published an important second peer-reviewed paper on our reanalysis of NPC in the NCI cohort (Marsh *et al.*, 2007a), and this was neither mentioned nor cited in the Expert Panel Report.

In particular, the Expert Panel Report failed to mention our main conclusion that 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 (Marsh and Youk, 2005; Marsh *et al.*, 2007a). Moreover, as we described in the latest findings of our independent study of NCI's Plant 1, 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).

Related to this single citation of our work, it is curious that while the Expert Panel Report on page 12 devotes a subsection to "Critiques of Nasopharyngeal Cancer in the NCI Industrial Cohort" (where Marsh and Youk (2005) is cited), the Expert Panel Report conspicuously does not include a parallel subsection "Critiques of Lymphohematopoietic Cancers in the NCI Industrial Cohort", where our corresponding reanalyses of these malignancies could have been presented and discussed (Marsh and Youk, 2004).

Given these egregious omissions of several of our peer-reviewed research publications pertaining to formaldehyde epidemiology, I believe that the NTP and its Expert Panel have failed their central objective of reviewing *all* the scientific literature available to them before making a final determination about listing formaldehyde under the RoC. It is scientifically inappropriate and irresponsible for the Expert Panel to selectively choose and rely upon only certain studies as it did in the Expert Panel Report.

Because our published research on formaldehyde epidemiology conducted at the University of Pittsburgh, Graduate School of Public Health, Center for Occupational Biostatistics and Epidemiology, was unfairly and inappropriately omitted from the Expert Panel Report, I reiterate below the key points and conclusions made in my October 26, 2009 written comments[2] and November 2, 2009 oral comments to NTP.

<u>Summary of Comments Regarding NTP's Inappropriate Re-classification of Formaldehyde as a *Known Human Carcinogen*</u>

In my 2009 written[2] and oral comments to NTP, I concluded 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 was supported by our extensive reanalyses of the NCI cohort data and our independent cohort study of one of the 10 NCI study plants, and by the 2009 release by NCI of

corrected analyses from their 1994 cohort follow-up. These new and compelling results cast considerable doubt on the scientific validity of NCI's findings and IARC's 2004 reclassification, and ultimately, and on NTP's reclassification of formaldehyde as a *known human carcinogen.*

Because the NCI cohort study and the 2004 IARC reclassification represented a substantial portion of the available epidemiological information that NTP relied upon to reclassify formaldehyde as a *known human carcinogen,* it was scientifically inappropriate and irresponsible for NTP to neither consider nor mention the findings of our extensive peer-reviewed research. Our findings strongly indicate that there is, at best, only limited evidence of carcinogenicity related to formaldehyde exposure and that many alternative explanations for a causal association, such as chance, bias or uncontrolled confounding factors cannot be ruled out. Thus, I believe that formaldehyde should not be reclassified from its current NTP listing as *reasonably anticipated to be a carcinogen.*

The specific points I made in my written and oral comments to NTP follow:

Specific Points and Conclusions Made In Written[2] and Oral Comments to NTP

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).

I remain hopeful that my above comments will alert NTP to recognize that the Expert Panel Report in its current form does not include all the available peer-reviewed epidemiological evidence regarding the carcinogenicity of formaldehyde and, as such, the Expert Panel Report does not represent a scientifically valid basis for reclassifying formaldehyde as a *known human carcinogen*.

If you have any questions or need additional information, please do not hesitate to contact me directly.

Sincerely,

signature redaction

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