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CERHR Director
NIEHS
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P.O. Box 12233
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Research Triangle Park, NC 27709

July 8, 2002

Re: Written Comments on April 2002 Methanol Expert Panel Report

Dear Dr. Shelby:

The American Forest & Paper Association (AF&PA) submits the following comments in response to the NTP Center for Evaluation of Risks to Human Reproduction's May 8, 2002 request for comments on the NTP-CERHR Expert Panel Report on the Developmental and Reproductive Toxicity of Methanol (the "Report"), 67 Fed. Reg. 30,942. AF&PA is the national trade association of the forest, paper, and wood products industry. AF&PA represents more than 300 member companies and related trade associations involved in growing, harvesting, and processing wood and wood fiber; manufacturing pulp, paper, and paperboard from both virgin and recycled fiber; and producing solid wood products.

AF&PA has a substantial interest in the assessment of risks presented by exposure to methanol, because naturally occurring methanol is released during the manufacture of wood products and wood pulp. AF&PA previously submitted comments, dated September 7, 2001 and January 11, 2002, on a draft of the Report. Forest products industry consultants offered oral comments during the Methanol Expert Panel's meeting on October 15-17, 2001. AF&PA also responded, on October 2, 2000, to CERHR's August 17, 2000 request for data to be reviewed by the Methanol Expert Panel.

AF&PA submitted extensive analysis of the potential for exposure to methanol emissions to create risks to human health and the environment, including adverse effects on human reproduction and development, in connection with its March 8, 1996 petition to EPA to remove methanol from the list of "hazardous air pollutants" under the Clean Air Act. Those materials were also provided to CERHR in AF&PA's October 2, 2000 submission. AF&PA strongly believes that this information, along with the additional information presented in the Report and in AF&PA's oral and written comments on the draft Report, demonstrates that sufficient data are

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available to conclude there is no significant risk of adverse effects on human reproduction and development from exposure to methanol via air pollution.

AF&PA believes that the information it previously provided contains important analyses that the Expert Panel needed to consider, and in fact the Report reflects consideration of some, but not all, of the points contained in AF&PA's analysis. The following comments suggest several areas in which AF&PA believes the Report should be modified to make additional or more accurate reference to the materials AF&PA has provided. In addition, a key expert analysis of the statistical significance of results reported in the principal methanol study in primates, prepared by Dr. David Hoel and submitted to CERHR on January 11, 2002, apparently was too late to be considered by the Panel, and this letter addresses the critical findings of that statistical analysis.

AF&PA urges the NTP staff to address these and other comments on the Report and issue a final NTP report promptly. Because methanol is widely used and is released to the environment in large quantities, accurate, comprehensive, peer-reviewed information on methanol's developmental and reproductive toxicity will be valuable to many parties. Moreover, EPA apparently is now relying in other contexts on the unrealistic assessment of methanol's developmental and reproductive toxicity contained in its denial of AF&PA's petition to remove methanol from the hazardous air pollutants list. That risk assessment concluded that methanol may cause reproductive or developmental effects at concentrations as low as 0.3 mg/m^3, which in turn would increase blood methanol concentration by only 0.006 mg/l (compared to a mean concentration from natural metabolism and diet of 1.8 mg/l and a standard deviation of around 0.7 mg/l).

Need to Recast Discussion of Developmental Toxicity in Light of Burbacher Study

The Report's discussion of the Burbacher study, sponsored by the Health Effects Institute (HEI), on methanol disposition and reproductive toxicity in adult females and offspring developmental effects following maternal inhalation exposure (References 52 and 143 of the Report), fails adequately to consider the limitations and shortcomings of the statistical analysis of the study. AF&PA believes that the Burbacher study does have substantial value for the Expert Panel's task, but that value is that the Burbacher study is a comprehensive assessment of the reproductive and developmental toxicity of maternal methanol inhalation which shows no meaningful adverse effects for exposures as high as 1800 ppm.

The Burbacher study itself, and especially the included HEI peer-review commentary, present findings that at most suggest areas for further research, rather than confirming any adverse effects on mothers or their offspring from exposure to up to 1800 ppm of methanol. A large number of tests were performed, and yet the analysis of variances showed no statistically significant difference between the control group and the exposed groups in any of these measures of reproductive and developmental toxicity. Only when the researchers performed *post hoc* "linear contrast" comparisons between various groups did any differences emerge. The HEI peer-review panel and AF&PA's experts have all concluded that these analyses could easily

identify apparently differences between controls and exposed animals merely by chance, given the small number of animals, the multitude of tests, and the variability of individual responses.

The statistical analyses in the Burbacher Study present the possibility of misconstruing random fluctuations as effects of methanol exposure. The information that might be used to corroborate statistically identified differences in fact tends to disprove the hypothesized effects. As the HEI peer-review commentary notes and AF&PA's experts stated even more strongly, the lack of clear, monotonic dose-response relationships, despite clear differences in blood methanol concentrations; the lack of consistency among cohorts, sexes, and tests; and the difficulty of explaining apparent effects in the 200 ppm group, where maternal blood methanol was only slightly elevated above background; all undercut any assertion that the study's potentially random events demonstrate an effect of methanol on reproductive or developmental health.

To help EPA understand the significance of Burbacher's observations, AF&PA retained a renowned biostatistician, David G. Hoel. Dr. Hoel has a Ph.D. in Statistics from the University of North Carolina at Chapel Hill. He is currently Distinguished University Professor at the Medical University of South Carolina. Previously he had a long association with the National Institute of Environmental Health Sciences, including serving as its Acting Director and the Director of the Division of Biometry and Risk Assessment. Dr. Hoel has served on numerous National Academy of Sciences committees and other U.S. government advisory committees and serves on the editorial board of numerous publications, including the *Journal of Statistical Computation and Simulation*, the *Journal of Communications in Statistics*, and the *Journal of Environmental Pathology, Toxicology and Oncology*.

The December 30, 2001 report from Dr. Hoel, which AF&PA submitted to CERHR on January 11, 2002, as well as his analyses previously submitted to CERHR by AF&PA, details the shortcomings in the statistical analyses and conclusions of the Burbacher study. Dr. Hoel's work demonstrates, as he stated in his September 7, 2001 written comments to the Panel, that the data generated by Burbacher "provide a good example of how a large number of statistical tests can produce a few inconsistent, but entirely expected, positive results even when the experiment is truly negative. Based on the sheer number of statistical tests that were employed by Burbacher *et al.* and their failure to adequately control the experiment-wide false positive error rate, we are forced to conclude that there is no convincing evidence for an effect of methanol exposure on the behavioral measures evaluated in these primates."

The HEI review panel discussion of the Burbacher study noted concerns about the statistical techniques applied and the failure to adjust for multiple comparisons. The Report itself noted these concerns and stated that "[m]ore insight may be provided by an independent statistical analysis...." (Report at 74.) Most Panel members recommended a reanalysis of the Burbacher study data, stating that a "more rigorous statistical evaluation that adjusts for multiple comparison may permit consensus as to whether there is evidence that methanol is a developmental toxicant in monkeys." (Report at 111.) Dr. Hoel has conducted such an analysis and it was provided to CERHR on January 11, 2002, but apparently it was never reviewed by the Methanol Expert Panel. That analysis requires revision of the Report's statements about the results of the Burbacher study and its significance.

Dr. Hoel has summarized his reanalysis of the Burbacher study data using statistical methods that are optimally matched to the study's experimental design, with appropriate adjustment of the false positive error rate for the multiple comparisons problem. He also performed analyses using non-parametric statistical methodology that is robust to departures from normality and equality of variances, to ensure that such departures do not invalidate any conclusions.

The results of Dr. Hoel's reanalysis of the Burbacher study data are clear-cut and consistent. There were *no* endpoints for which statistically significant effects were observed. Dr. Hoel's overall conclusion, which must also be the conclusion of the NTP staff, is that the Burnacher study "showed no reproductive or offspring developmental effects of methanol exposure." Given that a well-designed study tested many endpoints in a species very relevant for assessing potential toxicity in humans and found no statistically significant effects, even at exposures orders of magnitude higher than what humans are expected to encounter, provides sufficient basis for the final NTP report to conclude that there is minimal concern for reproductive and developmental toxicity from expected human exposure to methanol.

(We also note that the Report contains a statement, at the top of page 97, that is both a *non sequitur* and non-sensical: "Both the rodent and primate neurobehavioral outcomes do suggest alterations in cognitive function are consistent and subtle." The only neurobehavioral adverse effects observed in rodents was in the Weiss single, high-dose (4500 ppm) study--a possible effect in running in a wheel which appeared only when the results were analyzed separately by sex, and perhaps subtle effects in changing patterns of sequential response--which were also subject to the same lack of compensation for multiple testing that plagued the statistical analyses in the Burbacher study. (See Report at 72.) These effects were neither internally consistent, nor consistent with other neurobehavioral assessments in rodents, nor consistent with Burbacher's results in primates. The Burbacher study itself of course did not reveal any statistically significant effects when analyzed correctly, but even the HEI Report suggested that the effects Burbacher noted were not internally consistent (better performance in high dose group, differences between cohorts, inconsistency with other measures of similar functions, etc.). What the rodent and primate studies have in common is that only through multiple comparisons, with failure to adjust the statistical analysis to reflect those multiple comparisons, could subtle, inconsistent effects be coaxed from the data.

An additional point, also not reflected in the Report, is Dr. Hoel's previous analysis showing that the observed effect in the visually directed reaching test could be explained simply by the unusually long mean gestation period of the controls, which in turn was disproportionately affected by a single outlier that was delivered post-maturity. If gestational age rather than age since birth is used to determine how quickly an infant masters the visually directed reaching test, then no effect would be seen in the methanol-exposed group, even applying the statistical tests Burbacher used. An EPA Office of Research and Development scientist who reanalyzed the Burbacher study with that in mind concluded that there was in fact no effect of methanol exposure in that test. (See August 16, 2000 Memorandum from Jeff Gift to Mike Davis, "Comments on AF&PA methanol delisting petition submission dated July 3, 2000," at 3.))