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Dr. Michael Shelby, Director
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Dear ~~Dr. Shelby~~ Mike:

As a member of the Expert Panel for the CERHR-NTP Methanol Report, I wish to offer these comments on the final report dated April 2002. My commentary relates to both the content of the report and the process by which the report was prepared. In addition, my comments on the substantive aspects serve to highlight the main reasons for my formal dissent from Section 5 of the report. My intent is to offer constructive thoughts bearing not only on the Methanol Report itself but other reports that the CERHR may produce in the future.

One of my fundamental concerns about the Methanol Report pertains to risk communication. In Section 5.3, Overall Conclusions, the key message of the report is distilled to four bullet statements. These bullet statements may well be the only part of the report that many people will ever read. The statements indicate that, at blood methanol levels below 10 mg/L, the Panel had "minimal concern" about developmental toxicity in humans and "negligible concern" about male reproductive toxicity in humans. "Concern" (unmodified) is expressed about developmental toxicity if pregnant women are exposed specifically to "high levels" (undefined) of methanol. However, no expression of concern is registered regarding female reproductive toxicity, because of a lack of data. Most readers will interpret these conclusions as implying that essentially no concern is warranted regarding developmental or reproductive toxicity from methanol exposure in the general population. In my view, this is not the message the Methanol Report should convey. I say this for the following reasons.

First, the animal toxicity data on which the conclusions are based are, by the Panel's own characterization, "limited," "fragmented," "uneven," and, in some respects, "insufficient" (Methanol Report, p. 108). It is difficult to understand how one leaps from such limited data to confident assertions that essentially no concern is warranted about reproductive or developmental toxicity in humans from methanol exposure at other than "high levels." If the database were ample, robust, and consistent, then a conclusion of "no likely effect" might be warranted. That is not the case here. Instead of emphasizing the uncertainty of the available data, however, the Overall Conclusions offer assurances to the public and stakeholders, including those with a commercial interest in methanol fuels, that only "high" exposure levels, typically associated with accidental ingestion, pose a concern with respect to methanol toxicity hazards.

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Second, the Overall Conclusions imply that methanol exposures are either "low-level" (blood methanol concentrations below 10 mg/L) or "high-level" (blood concentrations unspecified). This false dichotomy fails to recognize the likelihood of population exposures that are intermediate, that is, higher than "low" but less than the high levels associated elsewhere in the report with accidental exposures, especially ingestion. This intermediate exposure segment likely comprises individuals who use methanol in hobbies (e.g., model airplane fuels) or as a solvent (e.g., for cleaning purposes); also, increased usage of methanol fuels for motor vehicles could greatly expand the percentage of the population exposed to intermediate levels of methanol. Such exposures may be of particular concern with respect to reproductive and developmental effects because the critical period of exposure sufficient to induce adverse outcomes could be relatively brief.

The effect of the dichotomy between low and high exposures is to foster the misleading impression that one need not be concerned about exposure to methanol unless one makes the unfortunate mistake of ingesting the substance. As I understand the CERHR guidance to the Expert Panel on formulating conclusions, the lack of empirical data on intermediate population exposures means that considerations about this portion of the total population cannot be incorporated into the Overall Conclusions, because it would be "speculative." It seems terribly paradoxical that a reasonable inference about the distribution of population exposure levels cannot be entertained, whereas an inference of essentially no concern can be justified on the basis of limited and fragmented data.

A third but no less important point relates to susceptible populations. Again, the CERHR guidance requires "hard" information about the existence of such populations before they can be included in any expression of concern about the potential health hazards of methanol. Acknowledging elsewhere in the report that "subpopulations of undefined size may exist" but not including in the Overall Conclusions any reference to groups having diminished metabolic capacity to handle methanol (as is well established for ethanol) seems to be yet another case of a double standard for what constitutes sufficient evidence. In effect, in the face of scientific uncertainty the Methanol Report, reflecting CERHR guidance, places the burden of proof on those who would advocate some caution regarding the potential toxicity hazards of methanol rather than on those who, in this instance, have claimed that methanol poses essentially no concern.

Finally, it is difficult to reconcile the fourth bullet conclusion regarding the insufficiency of data on female reproductive effects of methanol with the omission of female reproductive function from the list of Critical Data Needs in Section 5.4. Readers might well interpret this incongruity as implying that the Panel did not judge potential effects of methanol on female reproductive function to be a matter of concern, regardless of whether data exist or not. Presumably, this is not the message that the CERHR or the National Toxicology Program intends to convey.

The net effect of the above omissions and constraints is an understated expression of concern about the potential health hazards of methanol. I believe it would have been possible to articulate a judgment on this matter that would have been more scientifically accurate and reflective of the collective views of the Panel, as well as being more consistent with the "Guidelines for CERHR Expert Panel Members." The CERHR Guidelines document (p. 14) states: "Although strict categories of potential risk are not prescribed for use by the panels, the narrative conclusions should qualify the likelihood of an adverse effect under specified exposure conditions using terms such as unlikely, likely, or highly likely." Consistent with this guidance, the Panel's conclusions could have been stated in a more scientifically credible manner by saying, for example, "The Panel concluded that methanol exposures resulting in low (<10 mg/L) blood methanol concentrations are *unlikely* to result in developmental toxicity in humans." Additional qualification regarding susceptible populations would be necessary, but the basic statement is descriptive and easily understood by the general public. It also better reflects the reality that expert panels deal with weights of evidence and imprecise probabilities, not discrete categories of concern, or the lack thereof. In any event, my point is that satisfactory alternatives to communicate the Panel's collective judgment could have been adopted.

Although my comments thus far have been framed in terms of risk communication, I trust that they are understood as having significant implications for the substance of the Methanol Report and are not viewed as just fine points of semantics or word-smithing. If the CERHR reports are to serve a useful public health function, I believe it is very important to avoid overstating judgments about either hazards or lack of hazards. To avoid such overstatements, *uncertainty* – whether it pertains to susceptible populations, exposures, or some other factor – needs to be appropriately reflected in the final judgments of the Panel. To put aside scientific uncertainty in formulating the Overall Conclusions does not serve the public well.

My other major area of comment relates to the process by which the Methanol Report was created. I perceived a tendency among the panelists, myself included, to focus on their respective assigned areas. This is not unexpected, but it made it difficult to "see the forest for the trees" and made the actual meeting of the Panel less productive than it could have been. More interaction among panelists prior to the meeting would have counteracted the tendency toward a narrow division of labor and would thereby have facilitated accomplishing the ultimately most important task of formulating the Overall Conclusions. Interaction could have been encouraged by an explicit request from CERHR to the Panel to use E-mail communications addressing all members rather than having individual members interact only with CERHR or its contractor. In addition, one or more conference telephone calls could have been scheduled at appropriate stages in developing the draft document. Such interactions would not only have served as a stimulus for each individual to keep up with his or her own assignment but would also have provided an opportunity to see how different areas of the document compared and related to each other. Except for the difficulty in scheduling a conference call, these steps are simple and cost virtually nothing.

In addition, the Panel Meeting itself should include adequate time for the members to interact. In my experience with World Health Organization workgroups for Environmental Health Criteria and Air Quality Guidelines, a full week is typically scheduled for these meetings. Although the nominal scope of coverage may be greater in the WHO documents, the critical endpoints and key studies usually are not substantially different in number and extent from the material covered in the case of the Methanol Panel Meeting. An additional day or at least a half day would have probably enabled the Panel to identify, discuss, and resolve issues that eventually surfaced after the meeting last October. Even with more interaction through Email and conference calls prior to convening the Panel, at least three full days should be allotted for these meetings, in my view.

If these measures had been in place, the Methanol Report could have been completed relatively easily and quickly, I believe. However, in the face of several questions not only about the expression of the Overall Conclusions but about factual errors and omissions in Section 5, I was concerned and remain concerned that the process of resolving issues subsequent to the Panel Meeting needs to involve, and be open to, the entire Panel. As just one example, the missing pages from the 1986 NEDO report, which I identified and provided to the CERHR contractor, were evidently never provided to members of the Panel. The pages in question included a table showing reductions in brain weight in a two-generation rat study that had been replicated in a special ancillary study. Although it may be debatable whether these missing pages would have warranted a change in the Overall Conclusions, I felt they were significant enough to merit reconsidering the characterization of the NEDO study by the Panel. If nothing else, omission of this information creates the impression that the Panel failed to consider all relevant information. Addressing this matter would not have been difficult, costly, or time-consuming. On the other hand, some of the factual errors I noted in the Report after the October Panel Meeting were readily corrected. It is not clear why some of my recommended corrections were accepted whereas others were not. If the entire Panel were involved in, or at least kept informed of, the resolution of such issues, it would help avoid the appearance of being arbitrary in accepting or rejecting the views or recommendations of individual Panel members.

As noted above, one of the flaws in the Methanol Report, in my view, is that the Critical Data Needs section does not identify female reproductive function as a specific data gap, despite the Overall Conclusion that data for this endpoint are insufficient. I believe this incongruity occurred primarily because of the limited time devoted to identifying and discussing critical data needs during the Panel Meeting. I doubt that the Panel as a whole intended to omit female reproductive function as a critical data need, and it would have been a relatively simple matter to have the Panel consider this matter by Email after the meeting. However, communications to the Panel seemed to focus more on closure on the Report than on making sure the document was as accurate and rigorous as it could be. It is understandable that procedural kinks need to be worked out as the CERHR matures. However, in my view, procedures and schedules should never become an end in themselves and should not be allowed to outweigh the more important considerations of quality, credibility, and protection of public health.

I hope that you will find my comments on the substance and process related to the Methanol Report to be helpful and constructive. These comments reflect my personal views and do not necessarily represent the position or policies of the U.S. Environmental Protection Agency.

Sincerely yours,

J. Michael Davis, Ph.D.
Senior Scientist

cc: William Farland
Lester Grant