Final Written Comments

Toxicological Review of Methanol (Noncancer) (CAS No. 67-56-1)

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The comments below summarize my opinions regarding the extent to which the May 2013 version of the subject document incorporates and responds to key comments, recommendations, and suggestions I provided on the previous draft. These opinions are based upon my review of the original and revised reports, responses by EPA to my original comments provided in Appendix A of the revised report, public comments received as part of the review, and discussion among panel members during the teleconference that took place on June 26, 2013.

Overall, I found the revised report to be fully responsive to most of my comments and suggestions and partially responsive to others. Opinions on what I consider to be the more important comments and suggestions are presented first, followed by a listing of some lesser points that merit some follow-up comments.

Key comments and suggestions

1. In reviewing the original version, I noted, "The format of the document contributes to redundancies, and presentation of some topics is fragmented, forcing the reader to synthesize information presented in more than one section of the main document and appendices. This is a problem inherent in the current format for IRIS toxicological reviews. Sometimes subtle points are lost in the repetition. A great deal of information is needed in order for the analysis to be transparent, but this shouldn't get in the way of clearly highlighting key points and decisions. A different format could be much more effective in conveying critical information, interpretations, and decisions regarding available, relevant toxicological literature." (response to Charge Question D2).

The organization and presentation of the information is greatly improved, creating a much more readable document. The information seems to flow better, redundancies are minimized, and tables are used to more effectively summarize information. The document is highly responsive to my comment.

2. In responding to Charge Question A2 for the original report, I expressed concern about treating endogenous and exogenous methanol differently toxicologically when both contribute to the internal dose. In the revised report, this issue has been addressed by including species-specific background/endogenous methanol in the PBPK models. This approach makes a great deal more sense, in my opinion, and is consistent with the concept that risk is a function of internal dose, and that both endogenous and exogenous sources contribute to that dose. I consider this change responsive to my comment.

3. In responding to Charge Question B4, I noted that selection of the individual UFs appeared to be consistent with EPA guidance and practice, but that a strong case could be made for eliminating the database uncertainty factor. Public commenters have also questioned whether this UF is necessary given the extensive toxicity data available for methanol. In response to my comments and others, the revised document now explains more clearly the rationale for including a database UF of 3. In Section 5.1.3.2.3, the EPA acknowledges that the database for

methanol toxicity is "quite extensive," but points to the lack of a quantifiable monkey study to address uncertainties regarding species sensitivity to reproductive effects. They also point out that a full developmental neurotoxicity test (DNT) in rodents has not been performed. The better explanation of the rationale for a database UF of 3 is an improvement in terms of transparency, but I don't find the argument that convincing. It seems to me that the uncertainty contributed by limitations in knowledge about species sensitivity (per the monkey studies) has in effect been double counted in the overall UF. The absence of a full DNT test is rodents is stated to be important in part because of the critical effect of decreased brain weight in rats, but I still have reservations about the strength of that finding (see below). In short, the report is responsive in terms of providing a clearer case for a database uncertainty factor of 3, but I still question whether it is needed.

4. One of my strongest criticisms of the report was that the proposed toxicity values were counterintuitive, implying that individual with no unusual methanol exposure may be at risk of developmental effects. I noted that absent any explanation in the document why these values make sense, the results lacked credibility. (see response to Bonus Charge Question). The new proposed RfC and RfD are higher values, and the IRIS assessment addresses the issue of comparison of associated blood methanol concentrations with background levels directly. This is a very important addition to the document and helps place the RfC and RfD in perspective. This is an important step in the right direction, but the result is not particularly convincing in my opinion. There are a couple of issues. One is how background is defined. Nearly all of the studies used to obtain data in humans had restricted dietary intake of foods that might increase methanol levels. As noted by at least one public commenter, this perhaps provides data on methanol blood concentrations that can be expected from endogenous metabolism, but hardly captures the range of blood methanol concentrations in individuals consuming a normal diet. It presents a view of typical methanol blood concentrations that is arguably too narrow for the general population. If the statement in the current assessment that typical blood methanol concentrations are assumed to be without adverse effect (which I support), that presumably applies to the higher blood methanol concentrations that would be expected without dietary restriction. The second issue is the way in which RfC and RfD associated changes in blood concentrations are compared with background. The document contends that the magnitude of change produced by exposures at these doses/concentrations make them distinguishable from background and therefore potentially toxicologically relevant. I'm not sure that's the case. It appears that for a sizable fraction of the population, exposure at these doses/concentrations would not result in blood methanol concentrations outside the normal range, particularly considering the first point, above.

I think that the report represents progress in dealing with the problem of assessing risk from exogenous exposure to endogenous chemicals, but falls short of presenting a compelling case why the toxicity values are not excessively conservative.

Less Important Points

5. In the current assessment and in responses to comments, the U.S. EPA has more clearly and thoroughly described what it perceives as the strengths of the NEDO study, making a better case for its selection as the principal study. One of the major criticisms of the NEDO study was the use of multiple t-tests to compare treatments. In response to suggestions that the U.S. EPA reanalyze the brain weight data using more appropriate tests, the agency has responded that this is unnecessary because a more definitive benchmark dose analysis was conducted using the

data. I understand the contribution of the benchmark dose analysis for dose-response assessment, but it misses the point of answering the question of whether the NEDO study showed a statistically significant effect of methanol on brain weight. This issue should be addressed unambiguously in the report to eliminate concerns that the benchmark dose analysis might be modeling chance observations rather than methanol effects.

6. Charge Question A5 for the original report asked about the scientific justification for the extrapolation approach from rats to humans for *in utero* and neonatal lactational and inhalation exposure. My response was that the approach made two assumptions: 1) that maternal-fetal transfer is similar between mice and humans; and 2) that lactational and inhalation exposure is sufficiently similar that the same maternal/offspring methanol concentration ratios will be seen. I indicated that the first assumption is reasonable, but that the second one is highly uncertain. The U.S. EPA, in responding to comments, has stated that lactational and gestational compartments may be considered in future assessments but are not necessary for the current toxicological review. They continue to state in the current assessment, and reiterate in the response to panel comments from the original review, that the ratio of blood methanol concentrations between a human infant and its mother is not expected to be significantly different than the approximately 2-fold difference seen between rat pups and dams. The reasoning for this is ostensibly explained in Section 5.1.3.2.2, but I do not find a clear rationale there. The main point made in that section regarding this issue seems to be that this assumption isn't particularly important because most of the effects of methanol occur *in utero*. To the extent that it matters, the assumption that maternal/offspring methanol concentration ratios are similar in both humans and rats continues to be poorly justified in my opinion.