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Toxicological Review of Methanol (Non-Cancer)

FINAL COMMENTS

(1) Comments on Revised Document

* The revised (May, 2013) version of "Toxicological Review of Methanol (non-cancer)" has been improved significantly in comparison to its external peer-review draft (2011) version. It addressed the key recommendations, comments and suggestions provided in my Post-Meeting Comments of 7/31/2011.

While the revised PBPK model used in the derivation of reference toxicity values of methanol still contains many simplifications and shortcuts, it seems to be adequate for chemical-specific risk assessment - the purpose for which EPA developed this model.
The authors of the revised model version assured: "*The model adequately fits the experimental blood kinetics of methanol in rats and mice and is therefore suitable for simulating blood dosimetry in the relevant test species and routes of exposure (oral and i.v.)...*" (evidenced in Section B.2). Then, the re-parameterized and appropriately scaled model was shown to predict pharmacokinetics of methanol in humans (evidenced in Section B.2.6).

The PBPK model was structured and modified with the specific aim in mind, according to the rules of parsimony, and even its simplistic approach to the human physiology – especially the urinary output, seems to approximate realistically the quantitative clearance of methanol (although, the assumption that the urine equilibrates with mixed venous blood may be inappropriate for some other chemicals).

Suggestion: Please reconnect the urine clearance to arterial blood in the PBPK model.

* The methanol concentration in maternal blood was selected as a surrogate dose metric for dose-effect modeling of postnatal changes. Even though it seems to be technically acceptable, without the understanding of exact mechanism of action (MOA) the selection of such a surrogate dose metric remains somewhat speculative. While the issue of dose metric selection and lack of information on MOA have been used in the revised document to justify the uncertainty factor associated with interspecies extrapolation (UF$_A$), it seems that the incompleteness of the MOA database could be rather used to justify the uncertainty factor associated with deficiencies in the toxicity database (UF$_D$).

The authors of the document should be commended for breaking off with almost ten-year-old, scientifically indefensible U.S. EPA tradition of applying all uncertainty factors (UF) to the external human equivalent concentration (HEC estimate). Even if, within the validated range of a PBPK model, the pharmacokinetics of a chemical appears to be almost linear, by the virtue of potentially saturable mechanisms of absorption, metabolism and excretion - it is still prudent to apply UF$_A$, UF$_H$, or perhaps in this case UF$_D$, to the internal dose (paraphrasing Paracelsus:

"this is the **internal** dose that makes a poison"). While the inherently arbitrary selection of numerical values of UF_A, UF_H, and especially UF_D has been criticized in the Public Comments, their application to the internal dose metric is scientifically justifiable and correct. However, the suggestion in the public comments regarding the UF_A and UF_D, that: "*The lack of primate data should only be applied to one or the other, as this "double counting" adds yet another forced conservatism to the assessment*", seems to be valid.

Suggestion: Please use the incomplete primate data once - to justify only UF_A. Consider using lack of information on MOA to justify UF_D. Please adjust numerical values of both uncertainty factors (UF_A and UF_D) appropriately (perhaps, UF_A = 3 and UF_D = 3).

* The apparent controversy regarding the background/endogenous levels of methanol has been clarified in the revised (May, 2013) version of the document, and species-specific methanol background levels are now considered in the final PBPK modeling. The potential impact of human exposures at RfC and/or RfD levels in relation to endogenous methanol background blood distribution is presented graphically in Figures 5-3 and 5-4. While both figures seem to be persuasive visually, they lack an objective statistical analysis of significance.

Suggestion: Please provide statistical analysis of confidence limits/significance of RfC and/or RfD impact in relation to background/endogenous levels of methanol.

* The public comments questioned the values of metabolism parameters, V_{max} and K_M used in the PBPK model and suggested that EPA should implement a linear model. It seems that these suggestions are inappropriate.
Thus, the metabolism of methanol is potentially saturable and its kinetics is best described by a rectangular hyperbola [$y = ax/(b + x)$, where "y" is rate of metabolic reaction, "a" is maximum velocity, "b" is concentration of methanol necessary to get half of maximum velocity, and "x" is concentration of methanol]. By convention, the parameters of this equation for non-linear, saturable metabolism, are depicted in PBPK models by Michaelis and Menten terms: "V" for metabolic rate, "V_{max}" for maximum velocity and "K_M" for affinity (Michaelis) constant. The distinction between the Michaelis and Menten equation and the PBPK metabolic variable is, that while Michaelis and Menten equation describes initial velocity in homogenous enzymatic systems, the PBPK model describes rate of metabolism, measured over time in the whole organism. Therefore, it is prudent to use in PBPK models the terms: "pseudo-maximal velocity of metabolism" for "V_{max}" (usually in mg/h), and "apparent Michaelis-Menten constant of metabolism" for "K_M" (usually in mg/L). Obviously, depending on the timing and complexity of the modeled non-homogenous systems, the numerical values of both pseudo-maximal velocity and apparent Michaelis-Menten constant of metabolism of methanol may differ significantly, especially, that In the PBPK models both parameters are fit and adjusted by global optimization.

Suggestion: Please keep unchanged equation and parameters for methanol metabolism in the PBPK model, but change in the text the explanation of meaning of V_{max} to "pseudo-maximal velocity of metabolism" and K_M to "apparent Michaelis-Menten constant of metabolism".

(2) Suggested Additional Corrections:

* P. XViii; lines 10 - 11, state:
"*Because of its volatility methanol can also be excreted unchanged via urine or exhaled air*"
Change to:
"Because of its volatility methanol can be exhaled with air, and also excreted unchanged via urine."

* Page XViii; lines 19 - 20 state:
"*Specifically, new EPA models were developed or modified from existing models, to allow for the estimation of monkey and rat internal dose metrics*"
Change to:
"Specifically, EPA developed new PBPK models or modified the existing ones, which allowed for the estimation of monkey and rat internal dose metrics."

Figure 3-2:
Explain nonstandard abbreviations: "*AdoMet*" and "*AdoHyc*".
Please note, that S-adenosylhomocysteine is usually abbreviated to "AdoHcy" rather than "*AdoHyc*".