

**Department of Defense Comments on the  
Draft Final Toxicological Review of Methanol, October 2009**

Comments submitted by: Office of the Secretary of Defense Chemical and Material Risk Management Directorate

Organization: Department of Defense

Date Submitted: 23 November 2009

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1		Global	The draft toxicological review seems lengthy and complicated. Attempting to discern those data that have been extracted for use in estimating EPA's non-cancer and cancer toxicity values is difficult. The text, tables, and figures are neither clear nor transparent; some contain inaccuracies. The document appears to contain logical inconsistencies in different sections of the main text and appendices that seem to be disparate views among the authors. For this reason, some of the comments have been presented in an order other than that of their page number.	The document should contain a table or short summary of the major decisions and data used quantitatively for deriving the cancer and non-cancer risk values without reading all of the text and appendices.	E
2		Global	The document reads like an advocacy submission, rather than an unbiased review of the literature. Views and scientific opinions held by the majority of the experts and reports are dismissed without a clear presentation of their data and arguments, including misrepresentations of their statements and data.	Minority opinions and analyses should be presented and appropriately defended – but so should majority opinions. If both are presented in an unbiased manner, regulatory decision-makers and the public can determine the range of potential risks.	S
3		Global	The bioassay data used for the oral cancer potency factor are from a batch of studies that expert panels have determined are likely to be caused by infection rather than exposure to the chemicals on test. Based on this finding, both the Food and Drug Administration and the European Union (reaffirmed in 2009) have determined that the leukemias are not relevant for human risk assessment. Furthermore, this analysis uses nonconventional techniques and a physiologically based pharmacokinetic (PBPK) model that has not been peer reviewed to calculate	If nonconventional risk assessment procedures are used, the results of the standard EPA analysis should also be presented. If peer-reviewed models are modified, the results of the unmodified model should be presented.	S/M

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			toxicity values.		
4	4.6.5.2	4-82, 3	The European Foundation of Oncology and Environmental Sciences (ERF) studies have been highly controversial, for many reasons, not all of which are sufficiently explained in this analysis. Some of them are discussed in the next few comments. For example, as this document states, 8 of the chemicals tested have had high background rates of lymphomas, and these occurred at the same time period. The controversy about the causal factor for the lymphomas is particularly an issue for the chemicals that were tested at approximately the same time as the aspartame bioassay, which includes methanol.	The analysis of high background rates potentially due to an infection in the colony should be limited to those ERF studies during that time period.	S
5	4.6.5.2	4-82, 3	The overall, historical rate of lymphomas in the colony is irrelevant, if there was a temporal peak due to a laboratory infection. Moreover, most evaluators of bioassay data use the contemporary controls for the analysis. Use of historical controls is primarily for the purposes of explaining why an assay should not be used, e.g., because the contemporary controls are not consistent with the historical controls. In this case, historical averages appear to be used to ignore the high values of contemporary controls.	The inconsistent use of historical controls should be removed from the analysis. Moreover, as explained in a latter comment, the independent pathological review of this issue – that has been accepted by U.S. FDA and the EU – should be presented as the opinion that reflects the view of the majority of the scientific community. If these authors continue to believe differently than other, independent evaluations of the primary data, then it should be clearly labeled as a minority opinion.	S
6	4.6.5.2	4-83, 15	This speculation about alternative causes of the high background is interesting, but conflicts with the prior assertions by these EPA authors that there is	It is not logical to assert in the space of three pages that (1) "only 8" of over 200 bioassays have high background rates of lymphoma and (2) the ERF strain or study protocol produced	S

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			not a high background of lymphomas.	the high background rate. As the first does not address the issue raised by numerous academic, Federal, and international scientists, i.e., a contemporaneous infection of the colony, it is recommended that only the latter be presented. In that case, some data to support the assertion would be useful.	
7	4.6.5.2	4-87, 6	<p>While this document states that the conclusions of the European Food Safety Authority (EFSA) panel were that, <i>"the apparent compound-related increase in lymphomas and leukemias, may have been incidental findings and, therefore, unrelated to aspartame."</i>, the conclusions of the Pathology Working Group were much more definitive. As reported on the National Cancer Institute's web page (<a href="http://www.cancer.gov/cancertopics/factsheet/Risk/artificial-sweeteners">http://www.cancer.gov/cancertopics/factsheet/Risk/artificial-sweeteners</a>)</p> <p><i>"Shortly before this most recent study of aspartame and cancer was published, the European Food Safety Authority reviewed the recent animal data and urged caution when interpreting results (The European Food Safety Authority 2006): "The increased incidence of lymphomas/leukemias reported in treated rats was unrelated to aspartame, given the high background incidence of chronic inflammatory changes in the lungs and the lack of a positive dose-response relationship."</i></p> <p>Moreover, the FDA determined that the lymphomas</p>	<p>The lack of a dose-response relationship, noted by the EFSA and in Table 4-27, is a clear indication that the chemical exposure is not related to the effect.</p> <p>Since the regulatory toxicologists, pathologists, and risk assessors at FDA and the pathologists (mainly from NIEHS) agree, it seems counterproductive for EPA scientists to revisit exactly the same data but without the slides that were available to the Pathology Working Group.</p> <p>Similarly, since this document states that it can not verify which metabolites of methanol are responsible for the putative carcinogenic effects, rehashing the Soffritti (ERF) studies of MBTE and formaldehyde serves no purpose except, presumably, to "make the case" that the lymphomas are a result of chemical exposures, contrary to the consensus of national and international expert panels. As these are not complete reviews of the carcinogenicity of these chemicals, we</p>	S

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			and leukemias were not relevant for humans and did not use these findings to regulate aspartame.	recommend that they be deleted.	
8	4.9.2	4-104	Footnote 61 cites Curzan (2009) as a reference for combining " <i>lymphoblastic lymphomas, lymphocytic lymphomas, lympho-immunoblastic lymphomas and/or lymphoblastic leukemias as malignant lymphomas.</i> " In contrast to this statement, the actual quotation from Curzan is as follows [emphasis added]: " <i>The RF [Ramazzini Foundation] often combines the incidences of all cancers derived from blood-forming cells for statistical evaluation and calls them "hemolymphoreticular tumors" (Table 15). This is generally not considered appropriate, because different cancers are derived from different cell types and do not share a common derivation. The cancer diagnoses included in the "hemolymphoreticular tumors" were histiocytic sarcoma, mononuclear leukemia, myeloid leukemia, lymphoblastic lymphoma, and lympho-immunoblastic leukemia.</i> "	All references to other scientist's conclusions should be re-checked for accuracy.	S
9	4.9.2	4-106, 9	This document states that the lymphomas were challenged, " <i>because there is no indication that ERF used specific pathogen free (SPF) rats (Schoeb et al., 2009), and the protocol for the studies conducted by the ERF (Soffritti et al., 2002c) is different from 2-year bioassays conducted by NTP and NEDO.</i> " Both of the stated reasons are not quite accurate. The challenge is that the mouse colony was infected, as demonstrated by the lung pathology, i.e., not at the site of exposure. The use	To be fully correct, we recommend that the statement be edited. In particular, EPA should explain why they used a study that did not follow EPA guidelines to calculate the oral cancer potency.	S

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			of a colony that was not reliably pathogen free is a likely cause of the infection. If there had not been such a strong indication of an infection, the lack of specific pathogen free rats would be of less concern. Also, the ERF protocols are not consistent with <b>EPA</b> , <b>OECD</b> , or <b>FDA</b> guidelines, as well as <b>NTP</b> and <b>NEDO</b> guidelines.		
10	4.9.3	Pgs. 4-110 – 4-111	EPA's weight of the evidence is based on studies that have the same fundamental flaws and have not been repeated in other laboratories. Using questionable data to support a conclusion weakens EPA's analysis.	More robust and credible data should be used to support conclusions.	S
11	4.9.3	Pgs. 4-110 - 4-111	The assumption of concordance between methanol metabolites and formaldehyde concentration contradicts the later statements about (1) the lack of knowledge about the relative concentrations of the various methanol metabolites in humans and (2) the rapid metabolism of formaldehyde to formate. Moreover, if the lymphomas in both of these studies were contaminated by the same infection (the most widely held opinion), then the finding of a correlation is more likely based on the infection. Basing a cancer potency factor on an endpoint that has been consistently and repeatedly considered not to be related to exposure to the chemicals on test, is difficult to justify, except that it is the only data from oral exposures that are positive.	More robust and credible data should be used to justify conclusions.	S/M
12	5.4.1.3	5-32, 5	Although methanol metabolites gave the best fit of the three metrics, the conclusion in the appendix is	The text should be edited to reflect that none of the metrics fit the oral data well.	S

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			that even this metric was not a good fit, especially for the oral exposure data.		
13	5.4.1.3	5-32, 24	As described in more detail in the comments on Appendix E, the use of a default interspecies extrapolation factor after using a chemical-specific interspecies PBPK adjustment is not appropriate.	The points of departure for the extrapolation should be recalculated without a double adjustment for allometric interspecies scaling.	S/M
14	5.4.1.3	5-33, 10	Based on EPA's cancer potency factor and data from FDA's table on levels of methanol in carbonated beverages, a person drinking half a liter of soda a day should have about a one-in-one thousand risk of cancer (Table 24. Methanol Levels in Foods and Beverages. NTP-CERHR Expert Panel Report On The Reproductive And Developmental Toxicity Of Methanol, April 2002.)	Information such as this should be included since it can be a useful reality check and bounding exercise. It can also inform the decision-maker of the uncertainty inherent in the calculations.	S
15	5.4.3	5-37 Table 5-10	<p>EPA states that route-to-route extrapolation from Soffritti et al. (2002a) study would increase inhalation POD by about 4-fold.</p> <p>EPA states that the oral POD was based on the only tumor type from Soffritti et al. (2002a) drinking water study that had significantly increased (all lymphomas) while the inhalation POD was based on most sensitive tumor response from NEDO (1985/2008b) study that had an increased pheochromocytoma in female rats.</p> <p>If methanol is a systemic carcinogen, the two cancer potencies, i.e., the two HEDs based on appropriate PBPK modeling, would be expected to be virtually identical. Similarly, as the PBPK model and metric were assumed to be the same for both routes of</p>	Please explain the unexpected significant difference in types of cancers and cancer potencies, other than that it was the data they had.	S

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			exposure, the significant difference in types of cancers observed is not expected.		
16	B.1	First page of section, line 13	EPA modified the existing model. The modifications, including all of the additional assumptions required for these modifications, have not been peer reviewed. Lack of peer review of a PBPK model to help establish a toxicity value (for perchlorate) was one of the reasons EPA's Science Advisory Board (SAB) mentioned when it suggested that EPA recall its evaluation until the model was reviewed.	Until EPA's modifications are peer reviewed, results of using the other, already peer-reviewed models should be presented. EPA should not rely on the external peer review of this document to also peer review the model, as the latter can be an intensive effort itself.	
17	B.1	First page of section, line 13	EPA states, " <i>Renal clearance is a minor pathway and does not appreciably affect MeOH blood kinetics.</i> " Yet it added a renal compartment to the PBPK model and further states, " <i>addition of a bladder compartment ...impacts simulations for human urinary excretion.</i> " (line 18-19) These two statements appear to be contradictory. Since they are in the summary of the PBPK model, the reader is left to infer that the bladder compartment is required but does not have a significant effect. Such a conclusion does not inspire confidence in the model or those making the modification in the model.	The renal/bladder compartment should be kept in the model.	S/M

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18	B.1	Second page of section, line 5	Uncertainty factors (UFs) were applied to the internal dose and then the human PBPK model was used to estimate the human RfD. The human-equivalent NOAEL should be calculated using the PBPK model before the UFs are applied. As the PBPK model uses best estimate parameters, the <b>best of the internal dose</b> not the lower estimate on the dose should be used in the model. Otherwise, the uncertainty due to, for example, variability among people will be used with the best estimate parameters in the PBPK model.	All iterations of the PBPK model should be run with the data and parameters without adding the UFs. The appropriate UFs should be applied after the human-equivalent dose or concentration is estimated in order to calculate an RfD or an RfC or a cancer potency.  Please note that this is a <u>major</u> procedural issue for estimating toxicity values, it is strongly recommended that other IRIS documents be reviewed to determine if this has been a standard practice.	S/M
19	B.2.1	3 <sup>rd</sup> page of section, line 27	EPA states that the PBPK model <i>"only describes the rate of metabolism or conversion of MeOH to its metabolites. Distribution and metabolism of formaldehyde is not considered by the model, and this model tracks neither formate nor formaldehyde. (The data that would be needed to parameterize or validate a specific description of either of these metabolites is not available)."</i>  The toxicokinetics described in Chapter 3 and the PBPK models in this appendix indicate that the kinetics of formation of formaldehyde and formate in humans differs significantly from rodents. Indeed, mice differ from rats, and where data were lacking, the authors modified the human data to resemble mice rather than rats. For example, the human data were "linearized" in Figure B-20, page 330), even though it was clearly nonlinear, and the model required combining a fast and slow metabolism in	We recommend that if data are available to support this crucial issue, they should be clearly presented. Moreover, assumptions that minimized the well-known differences in rodent and primate metabolism of methanol should be eliminated, and the toxicity values recalculated based on models and data that retain these differences.	S/M

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			<p>order to fit the data, e.g., as described in Table B-1. The assumption that formaldehyde and/or formate are quantitatively the same "methanol metabolites" in the same ratios in rodents and primates is critical to EPA's analysis. However, the data presented by EPA repeatedly refute this assertion more than support it.</p>		
20	B.2.1	First and second paragraphs below Figure B-1	<p>Even though a bladder compartment was required and added for the human PBPK model to fit the data, nevertheless, the authors adjusted the value generated by the model because they assert (without proving) that the model will not correctly estimate this value. This results in estimating the larger animal (human) to have an even larger risk than that which they have gone to great lengths to estimate using a complex model for differences in kinetics</p> <p>As stated at the beginning of this document, the default factor of <math>BW^{3/4}</math> for interspecies adjustment is to be used in the absence of chemical-specific data. This is affirmed in EPA's document on use of this factor for oral, non-cancer, interspecies extrapolations, whose stated intent is to conform with oral cancer, interspecies extrapolations. In the case of methanol, not only is there an abundance of</p>	<p>As there is no need for use of an interspecies default factor for methanol, it is strongly recommended that all mention of this default factor be eliminated from this document. The analyses that use chemical-specific adjustments as well as the default should be changed to eliminate this second adjustment for interspecies differences. We recommend that any analysis that only uses this default should be eliminated from the document.</p> <p>The apparent lack of concern about applying a default factor after already performing the same adjustment on a chemical-specific basis raises concerns about analyses for other chemicals. It is recommended that they be reexamined and adjusted if necessary.</p>	S/M

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			chemical-specific data, there are also several PBPK models – the preferred method for interspecies extrapolation.		
21	B.2.1	Global	The authors assume that the PBPK model can be run without taking into account the existing level of methanol and formate in the blood due to normal human and rodent metabolism. This assumption is sufficient to invalidate the "validity checks" and sensitivity models. The body does not distinguish the source of these chemicals. For example, if the kinetics saturate at a blood level of $x$ and the normal level in the body is $x_0$ , then the standard assumption would be that an exposure greater than $(x - x_0)$ would saturate the kinetics. The assumption made by the EPA authors is that exposures would have to reach $x$ before the kinetics are saturated, thus assuming saturation occurs at a higher level that is accurate.	We recommend that background level of a chemical produced by the body must be taken into account.	S
22	B.2.2	Table B-1	In Table B-1, again the authors use $BW^{3/4}$ to scale the parameters – and plan to use it again after running the model.	See comment page 294, line 35.	S

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23	B.2.3.1	First page of section, line 21	The sentences at the end of this paragraph seem to be saying that absorption from the stomach is saturable and based on the volume of the stomach. The assertion is made that the stomach volume is proportional to body weight, rather than an allometric scaling of $BW^{3/4}$ , except that the value for mice will be kept the same as rats, even though (according to Table B-1) rats are 10 times the weight of mice. The data won't fit their assumption when scaling from a 0.03 kg mouse to a 0.3 kg rat, but the authors assume that it will be accurate for scaling from the 0.3 kg rat to a 70 kg human, and that it is appropriate to scale from a 0.03 kg mouse with a 0.3 kg rat's stomach to a 70 kg human.	This assumption should be changed to conform to the data. The toxicity values that depend on this assumption should be recalculated.	S/M
24	B.2.3.1	Text above Figure B-5	The scientists who produced the data and developed the model found that the volume of distribution varied with dose. However in this Toxicological Review of Methanol it was assumed that the scientists running the experiments and developing the model made an error when they were dosing the animals without any proof that a mistake was made by the scientists in the laboratory. External peer reviewers of the manuscript, that was published, indicated the necessity to modify the initial model based on the data. This is a very significant comment that was not considered in this document.	The peer-reviewed model and data should be used as presented unless EPA can present data that a laboratory mistake was made.	S/M
25	B.2.3.4	Global	As the analysis assumes that the concentration of formaldehyde or formate is the internal dose	If these assumptions are not accurate the effects on the estimated toxicity values should	S

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			responsible for adverse effects, this concentration is also the correct metric on which to base the interspecies conversion. As stated in this paragraph, however, these concentrations are never estimated. The analysis assumes that methanol clearance is equivalent to formaldehyde and formate production, but EPA states that " <i>this has not been verified.</i> " The limited data provided, the tables in Chapter 3, do not appear to support this assumption that is critical for the dose-response modeling. Moreover, Section 3.1 states that rodents have <i>two</i> pathways for formate metabolism, while primates have only <i>one</i> . Even if all of these pathways are "fast" and kinetically "favorable" one can not assume they are equivalent or that they produce equivalent ratios of all of the metabolites. Assuming the Tables 7-9 are actually Tables B-7 to B-9, these tables that are assumed to support this hypotheses have at least one value that is not accurately reported (see comment below for pages 386 & 387).	be presented, as should calculations based on equally valid assumptions.	
26	B.2.8.1	Global	In this section, the authors appear to simply remove the second metabolism compartment from the human model as unnecessary at low doses. As they assert in the second page of text in the section, " <i>A simple linear model is preferred over the use of a Km value that is high.</i> " The authors of this analysis may prefer a simple model; the scientists who developed the model and added this compartment apparently disagree. Moreover, this "simplifying	The results of using the model as intended by the developers (that retains this known difference between rodent and human metabolism) should be presented.	S

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			assumption" serves to make the human model more like the rodent model, i.e., less accurate for portraying the interspecies differences that it was designed to determine.		
27	B.2.8.1	Para. Following Table B-2	Even if the previous statement about subtracting background were accurate, EPA did not simply subtract the background. As stated in this section, the blood concentrations of the exposed population "were corrected by subtracting time-zero value for the exposed group plus a time dependent factor obtained by multiplying the slope of this regression (0.093 mg/L-hr) by the measurement time." Clearly, the role and importance of background levels of methanol and formate are not as simple as presented in this document.	If non-standard processes are used, the results of standard processes should also be presented.	S
28	B.2.8.1	Text following Table B-3	The authors state, "At greater than a 99.95% confidence level, using 2 metabolic rate constants (Km and VmaxC) is preferred over utilizing a single rate constant." The conclusion of this paragraph is that the nonlinear Michaelis-Menten model must be used as the human equivalent concentrations, "are being conducted in a concentration range in which the nonlinearity has an impact."	The analysis presented here appears to contradict the analysis presented on page 320. This logical inconsistency should be resolved and the toxicity values that depend on it should be recalculated, if necessary.	S
29	B.2.8.1. and Table B-5	Para. following Table B-5	After altering the PBPK model, the decision was made not to use this model and the actual conditions of the bioassay to determine the human equivalent concentration, but rather to use an algebraic approximation and the assumption of a continuous, 24-hour exposure for the interspecies	The assumption of a 24-hour, continuous exposure to methanol needs to be justified, as the animals were not exposed continuously, nor would people be expected to be exposed continuously.	S

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			conversion.		
30	B.3.8	Figure B-24, Table B-9	If Figure B-24 is correctly labeled, then the Cmax for 0.1 mg MeOH in a bolus should be almost 0.08 instead of almost 0.06, as reported in Table B-9. Since a time-dependent dose for only one dose level is provided, the rest of these data can not be critically evaluated.	Please check the accuracy of the remaining data since the only one presented appears to be incorrect.	S/M
30	B.2.9	First page in section	The text states: " <i>Mouse, rat, and human MeOH PBPK models have been developed and calibrated to data in the open literature. The model simplifies the structure used by Ward et al. (1997) while adding specific refinements (e.g., a standard lung compartment and a two-compartment GI tract). ... The model fits to the mouse oral-route MeOH kinetic data using a consistent set of parameters (Figure B-4) are reasonably good but not as good as fits to the inhalation data.</i> "  In the end, the fit wasn't that good, especially for the oral data.	The text should elaborate on whether the fit would have been better if the model and data had been used without changes.	S