Department of Defense Comments on
1,2,4- and 1,3,5-Trimethylbenzene Interagency Science Consultation Toxicological Review and Appendices

Comments submitted by: Chemical Material Risk Management Program	Organization: Department of Defense	Date Submitted: 2/9/2012

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	General		DoD believes that the EPA draft trimethylbenzenes (TMB) Toxicological Review represents a significant positive change in format and readability.	N/A	S
2	Preamble 2	7	EPA 2009 is not included in the list of references.	Add the reference to the list in Section 3.	E
3	Preamble, 3.3	8 - 9	Although this section explains the preferred types of exposures, the section does not contain definitions or examples. These definitions in the IRIS glossary are subject to change without notice. DoD would like to see contemporaneous definitions of "acute", "subchronic" and "chronic" exposures for both commonly used laboratory animals and people; these could be presented in a table.	Please supply definitions and examples of acute, subchronic, and chronic exposures for people and for all of the species that are used in the quantitative analysis of these chemicals.	S
4	Preamble, 4.2	9	In evaluating the quality of an epidemiological study, EPA does not include the need to demonstrate a reasonable dose-response	EPA should discuss its criteria with regard to dose-response observations for epidemiological studies. DoD notes in particular an over-	S/M

			relationship. As dose-response relationships are fundamental to all, high quality toxicological studies, this requirement, and whether the data must show a positive trend, a statistically significant increase, a biologically significant change, and/or other criteria should be presented in this section.	reliance on statistics rather than biologically informative information, as well as an absence of a discussion about dose-response criteria.	
5	Preamble, 4.3	10	In the third paragraph, EPA should state that it will clearly identify that its interpretation of the data differ from the scientists who conducted the study, as well as discussing why its conclusions differ. DoD would prefer if EPA would also commit to trying to contact at least one of the authors to determine their reaction to EPA's interpretation, and to allow those authors to comment on EPA's interpretation of the data, as they may have additional information about the study that was not published.	Disagreeing with the conclusions of the scientists who designed and conducted an experiment should only be done when there are clear and undisputed reasons. We suggest that EPA consider discussing its intended reinterpretation of the data with the authors before relying on a different interpretation for estimating toxicity of a chemical.	S
6	Preamble 5.2	11	DoD disagrees with EPA's statement that "causality is not at issue in controlled experiments". Unless a well designed experiment has been replicated exactly (often not the case for the critical experiment on which EPA bases its RfDs, RfC, and cancer potency values) statistically significant results can be false positives. At $p = 0.05$, there is a 1 in 20 probability of a false positive, even in a well controlled experiment.	EPA should delete this clause or provide at least one independent reference that would support its assertion.	S/M
7	Preamble 5.3	12	EPA's use of the term "genetic toxicity" is not	We highly recommend that EPA define "genetic	S/M

			defined and is neither clear nor transparent, especially in a section on mode of action (MOA). EPA's 2005 cancer guidelines and guidance do not use this term, but rather refer to a "mutagenic mode of action". Frequently, genetic toxicity includes effects that are not considered mutations, the term used in the rest of the document. DoD has previously mentioned EPA's tendency to use the terms "genotoxic" and "mutagenic" loosely, and as these terms have significant implications within EPA's guidelines and guidance, we would like to see more precision in their use.	toxicity" and "mutagenicity" (or variants of those words), as they have significant implications within EPA's guidelines and guidance. The IRIS glossary does not include a reference for "genetic toxi8city" or "genotoxic"; and it does not always agree with definitions in other parts of EPA's web sites and can be changed without notice or review.	
8	Preamble 5.4	12	The text does not mention a critical clause of the 2005 cancer guidelines: That the WOE for a chemical's MOA can vary by route of exposure or by level of exposure, etc. This section would be interpreted by many individuals as asserting that only one WOE is possible per chemical per endpoint.	EPA should include important options within this WOE section to clearly and accurately represent what is in its guidelines. The text should explicitly state that there can be more that one WOE for carcinogenicity, e.g., a chemical's MOA can vary by route of exposure or by level of exposure, etc.	S
9	Preamble, 7.3	14	EPA states that the choice of point of departure (POD) is based on statistical and biological factors and cites the draft BMD guidance (U.S. EPA 2000b) and EPA's 2005 guidelines for carcinogen risk assessment. The text goes on to state that for dichotomous responses, a 10% response will be used for "minimally adverse effects" and "5% or lower for more severe effects." Neither of the cited references have statements that agree with EPA's assertion.	This language should be removed from the current Preamble and instead included in the BMD guidance document; such recommendations can be proposed by EPA and formally evaluated by the scientific and regulatory community. EPA should also correct the citations of EPA2000a vs. 2000b.	S/M

			Both documents indicate that the benchmark response (BMR) that determines the POD should be near the low end of the range of data and that a 10% BMR should also be estimated for facilitating comparisons across chemicals. These concepts are also applied to the suggested methods for calculating the POD from continuous data. We know of no such severity-related guidance regarding the POD for nonlinear extrapolations in either of these documents. The definition of "minmally adverse" or "more severe" is a key aspect of the POD, but there is no available guidance as to how different effects should be categorized. Furthermore, the BMD guidance is listed in the references as U.S. EPA 2000a, rather than 2000b.		
10	Preamble 7.3 and 7.4	14	These sections, that cover standard procedures used, contain several statements that are not consistent with EPA's 2005 cancer guidelines. If IRIS is proposing that these statements are standard practice within its toxicological review, it should both state that these are deviations and should provide a rationale for its deviation from guidelines. We believe that the cancer guidelines are applicable to the entire agency. 1. None of the cited EPA guidelines or guidance suggests use of a "standard value" for a point of departure for extrapolation, much less "(10% response	This section should be carefully reviewed to ensure consistency with EPA guidance and the references cited. 1. Please delete any reference to a standard response level or value for a POD for extrapolation. EPA's draft BMD and cancer guidelines refer to use of standard values for the purposes of comparisons among chemicals, and in that case the best estimate, not the lower confidence value, is recommended for use. 2. The use of the lower bound should be	S/M

			for animal data, 1% for epidemiologic data, depending on the observed response rates)." These values are recommended as frequently used based on historical observations of results and the power of the standard studies. They are also recommended to be estimated and reported for the purposes of comparing potencies across chemicals. The phrase that is in EPA's guidance is "near the low end of the observable range is used" which will differ by experimental design. 2. The statement that "For dichotomous responses, the point of departure is the 95% lower bound on the dose associated with a small increase of a biologically significant effect." requires addition of the qualifier "generally" or "usually" to be consistent with the cited sources. In particular, the BMD draft indicates that the maximum likelihood estimate should be used for some purposes. 3. EPA's guidelines discuss use of a biologially based model to extrapolate to lower doses. They do not advocate "Below the range where confidence bounds on the predictions are reasonably precise, extrapolation may continue using a linear model."	qualified, as it is in the cited references. 3. According to EPA's cancer guidelines, use of a biologically based model obviates extrapolation; linear or nonlinear. The statement should either be deleted or clearly explain that IRIS is deviating from EPA guidance and provide a rationale for this deviation. 4. The concept of a "linear component" or "other activity" as a criterion for determining whether the extrapolation is linear or nonlinear should be deleted as inconsistent with EPA's guidance. Otherwise, the text should clearly explain that IRIS is deviating from EPA guidance and provide a rationale for this deviation. 5. The suggestion that exposure levels are a criteria for type of extrapolation should either be deleted or EPA clearly explain that IRIS is deviating from EPA guidance and provide a rationale for this deviation. 6. IRIS documents should define the terms "genetic toxicity" and "mutagenicity", how they differ (if IRIS scientists believe they do), and how these definitions relate to EPA's mutagenic mode of action.	

			4. EPA's 2005 cancer guidelines differentiate low dose extrapolation procedures for MOAs that are linear at low doses, MOAs that are nonlinear (including nonlinear, no threshold) at low doses, and chemicals for which the MOA cannot be determined. They do not provide for a linear extrapolation "the doseresponse curve is expected to have **a linear component** below the point of departure. [emphasis added]" . As many highly nonliear function have a "linear component" or can be fit to curves that have a linear component, this statement directly contradicts both the text and the intent of EPA's cancer guidelines. (DoD notes that the concept of a linear component is discussed with regard to chemicals with multiple MOAs, but does not make that a condition that requires a linear extrapolation.) 5. EPA's assertion that "Agents or their metabolites for which human exposures or body burdens are near doses associated with key events leading to an effect." is not included in the cited guidelines. IRIS has often asserted that IRIS documents do not consider exposure levels. If this is accurate, such a		

			consideration is not relevant to this document. If IRIS documents do consider exposure levels, this introduction should discuss those aspects of EPA's cancer guidelines that do refer to exposure, e.g., different WOEs for different levels of exposure. 6. The statement that "the agent does not demonstrate mutagenic or other activity consistent with linearity at lower doses." is not part of the criteria in EPA's cancer guidelines for using a non-linear extrapolation. The guidelines state that chemicals with a mutagenic MOA, not just mutagenic activity, are expected to have a linear extrapolation. This statement asserts a much lower criterion for imposing a linear extrapolation. Nor do the guidelines reference "other activity consistent with linearity" as a measure. The guideline only discuss such concepts within the context of the MOA, not individual key events of the MOA.		
11	Preamble 7.5	15	Statement #3 is incorrect. The cited EPA guidance document recommends use of the age-dependent adjustment factors ONLY for chemicals that have been demonstrated to have a mutagenic MOA that do not have chemical-specific data on early-life exposure, not	EPA should correct this misstatement of policy.	S/M

			"suspected carcinogens" as stated here.		
12	Preamble 7.6	15	EPA states that "if the point of departure is based on toxicokinetic modeling, dosimetry modeling or allometric scaling", UFA = 10^0.5 is applied to account for "the remaining uncertainty involving toxicodynamic differences." The U.S. EPA (2011b) guidance states (p 21) that "processes pertinent to the consideration of this UF are recognized to include both toxicokinetics and toxicodynamics." While IRIS has instituted a "common practice" of asserting such a division after PBPK modeling, it should either provide a written citation for this practice, and indicate whether it has been externally peer reviewed, or explicitly state that this is an IRIS-developed policy that has or has not been externally peer reviewed. If such a guidance document is prior to 2011, it should also provide a rationale for not following the more recent guidance.	EPA should revise the text to accurately reflect U.S. EPA (2011b) guidance.	S
13	Preface, Executive Summary, Literature Search	20, 23, 26, 29	The table numbering goes Table 1, Table II, Table 3, Table IV.	EPA should pick a format (Arabic or Roman numerals) and implement it consistently. DoD would prefer if this and other editorial errors were corrected prior to interagency review, as they increase the difficulty of finding material within the document and understanding the structure of the document.	E
14	Preface, Programmatic Interest	21	It is stated related isomers, 1,2,3-trimethylbenzene is not included in the review. This is one of the components of mixture of	Suggest adding a brief explanation for not including 1,2,3-trimethylbenzene in the toxicological review.	S

			three isomers.		
15	Executive Summary	21	We noted that the previous TMB PPRTVs not referenced nor discussed as “Other” Assessments.	Please provide a brief discussion of the previous PPRTV values. This is especially important given the differing conclusions and the fact that if finalized, the toxicity values derived herein will replace the PPRTV values. These documents are available to the public and should be addressed in the IRIS assessment.	S
16	Executive Summary	22	The first heading suggests a summary of effects following inhalation exposure to 1,2,4-TMB only, however discusses data, or lack thereof, for both isomers.	EPA needs to clearly match document Headings to the isomer discussion within. Please add “1,3,5-TMB” to the first heading for clarity.	E
17	Executive Summary	22	The statement “No human studies were found for 1,3,5-TMB” is not accurate, as 1,3,5-TMB exposure was part of the occupational cohort for Norseth et al (1991), (Appendix A.2 pg 48), and is a known constituent of the solvent mixtures from Battig et al (1958). Additionally, Jarnberg et al (1996), Kostrewski et al (1995, 1997), and Jones (2006) studied human volunteers exposed to 1,3,5-TMB and CNS-type effects were evaluated.	Clarify the statement if the intended meaning was that no human studies *providing adequate toxicological information* were found for 1,3,5-TMB. Although, it is not clear that the 1,3,5-TMB studies are any less informative than those for 1,2,4-TMB. Particularly, Battig et al (1958) should be added to the assessment (it was discussed in the respective PPRTVs).	S
18	Executive summary	22	It is not true that no human studies were found for 1,3,5-TMB. While Kostrzewski et al. (1995) primarily reports toxicokinetic data, it is noted in this paper that no effects were observed upon follow up.	EPA should revise the text.	S
19	Executive	22	It is not clear why EPA has chosen to assess	Please provide some rationale as to why 1,2,3-	S

	Summary		only 1,2,4- and 1,3,5-TMB, not 1,2,3-TMB.	TMB is not also assessed.	
20	Executive summary/global	22,23	The text is inconsistent regarding the use of superscripts, or in-line use (e.g., 10-2 mg/m3).	Superscripts should be consistently used.	E
21	Executive Summary	23	The UF for database insufficiencies should be reduced to 1. Two reasons are given for the deficiency. The first reason is the lack of a chronic study. However, EPA has already used a UF of 10 to account for this deficiency. Therefore, including it here is double counting the deficiency. The second reason is the lack of a two-generation study. As the one-generation study showed NO effects at doses that were below those that caused maternal toxicity and as the effects observed were relatively minor and related to maternal toxicity, i.e., both had less weight gain that are known to be associated, most toxicologist would find the conducting of a two-generational study redundant, and wasteful of resources (including many animals), as no effects would be expected. Reduction to 1 would be consistent with procedures outlined in EPA's RfD/RfC guidance.	EPA should reduce the UFD to 1.	S/M
22	Executive Summary	23	DoD does not understand why the confidence in the critical study is "medium" as all of the characteristics of the study (as reported) appear to be according to guidelines. Similarly, given our comments on reducing the UF on the	EPA should definitely change the confidence in the critical study to "high" or present the reasons for considering it "medium". If EPA agrees with DoD on reducing the uncertainty factor for the RfC, EPA should reconsider the overall	S

			database to 1, we believe the confidence in the database for the RfC should also be "high".	evaluation of the database.	
23	Executive summary	23, 24, 26	UFH and UFS are unnecessarily large. We will amplify our comments below (p 71). It is not appropriate to cite the lack of a chronic study as justification for UFD (p 23 and 24) because this gap is captured in UFS.	Conduct a sensitivity analysis of human PBPK model predictions for the key internal dose metric to better inform the selection of UFH, reduce the value of UFS, and revise the justification for, or value of, UFD.	S
24	Executive Summary	24	DoD does not agree that the combined UFs would be 10,000. First, the previous comments about double-counting the lack of a chronic study and the inappropriateness of requiring a two-generational study when the one-generational study showed minor effects in maternal toxicity are also appropriate here. That would reduce the combined UF to 3,000. The data presented in Appendix B demonstrate that the UF of 10 for a NOAEL to a LOAEL is unnecessary as well. The data for this isomer fit the benchmark dose as well as that of the other isomer. Therefore, a BMDL would be used as the point of departure, and the composite UFs would be the same as the previous, either 1,000 or 3,000 depending on whether EPA agrees with DoD with regard to the completeness of the database.	As the data for both isomers is apparently of equivalent quality, we recommend EPA estimate the RfC for 1,3,5-TMB from its data rather than inferring it from 1,2,4-TMB.	S/M

25	Executive summary	25	A period is missing near the end of the first paragraph.	Revise "same research institute Overall..." to read "...same research institute. Overall..."	E
26	Executive Summary - Section 1.1 - Appendix A.2		There is significant discrepancy between the studies listed in the Executive Summary, those discussed in the endpoint-specific Hazard ID sections, and those summarized in Appendix A.2. DoD cannot find the Appendix Study Summary information for Battig et al (1956)/MOE (2006) (listed as studies of human exposures to 1,2,4-TMB). EPA is missing Battig et al (1958), which was used in the previous PPRTV so must exist in the translated form somewhere. Billionnet et al. (2011) is summarized in Appendix A.2., but not listed in the Executive Summary or Section 1.1. Lammers et al (2007) is summarized in the Appendix under the “summary of animal studies” only; the human summary and study information should be broken into a separate study summary and be located in the human study section.	Please correct these reference errors and make sure the document is properly QA/QC’d.	S/M
27	1.1		DoD appreciates EPA’ effort to synthesize the toxicological data and provide an integrated summary of information, HOWEVER, EPA needs to still provide some of the basic information for each study and should immediately direct the reader to the Appendix for detailed study summaries. For example, dose-	Please add a few more details to the integrated hazard identification synthesis and reference the specific Appendix section that fully describes the study.	S

			ranges could be replaced with specific dose/concentrations administered, and sex/species information could be given where appropriate. It would be helpful to reference the Appendix study summary (explicitly with page number) the first time a study is mentioned.		
28	1.1.1	25	Given that a lack of a suitable oral study (for either compound) is a significant database limitation, it is not clear why EPA did not have the Koch Industries (1995) study, the basis for the 2009 1,3,5-TMB PPRTV "Appendix Oral screening value", peer-reviewed.	EPA should obtain a peer-review of the Koch Industries (1995) oral 1,3,5-TMB study. Further, the resulting chronic RfD of 0.01 mg/kg-day (derived in the 1,3,5-TMB PPRTV), should be compared to and discussed relative to the route extrapolated and isomer-adopted draft RfD of 0.006 mg/kg-day.	S/M
29	1.1	32	While EPA does a good job at the integrated discussion of endpoints and the respective potential MOAs, the discussion on neurotoxic effects, in particular, does not highlight that all of the available information is circumstantial; a full functional observation battery is missing and the toxicological significance of most of the animal data is questionable with significant uncertainties and limitations within the respective studies (only one species, one sex, same laboratory, etc).	EPA needs to make sure that an endpoint is presented in an unbiased manner: the available neurotoxicity data is weak with significant uncertainties and limitations in each individual study.	S
30	1.1.1	33	In various places throughout the text, EPA mentions that the decrease in pain sensitivity measured in Korsak and Rydzynski 1996 did not persist two weeks after exposures were terminated. And in fact, the table shown in	DoD does not feel that the uncertainties and limitations in Korsak and Rydzynski 1996 are appropriately discussed. Reversibility in the neurobehavioral effects is not adequately considered in EPA's interpretation of the data.	S/M

			Appendix A.2-5 (pg 54) clearly shows the loss of effect (only the high-dose was tested for persistence). Yet, this possible “reversibility” of the effect is not adequately discussed and may, in fact, make this study/endpoint not suitable for chronic toxicity value derivation. Derivation of the RfD/C based on a shorter-term exposure requires the consideration of reversibility in the interpretation of the data. Korsak and Rydzynski 1996 was dismissed as a potential principal study in the 1,2,4-TMB 2007 PPRTV due to “unclear toxicological significance” and “concentration-responses are difficult to interpret.”	Further, given the apparent reversal of the effect and other limitations of the study, we suggest that EPA reconsider Korsak and Rydzynski 1996 for RfC/D derivation.	
31	1.1.1	34	EPA makes inconsistent statements regarding the relative severity of the two TMB isomers (cf. pages 24, 58).	The text should be revised to be consistent.	S
32	1.1.1	35	Further explanation is needed regarding how the open field test results suggest latency. Presumably the authors mean that after 25 days, complete clearance of 1,2,4-TMB is expected, but this rationale and the authors' rationale for why they did open field testing at that time should be explained.	EPA should more clearly state the rationale for this statement, rather than expecting the reader to infer this significant comment with regard to assessing toxicity.	S
33	1.1.1	36	The first couple of sentences on this page are potentially confusing and neither clear nor transparent.	Reword the first part of the sentence to state "...exposure to 1,2,4-TMB or 1,3,5-TMB alone" to more clearly indicate the distinction from exposure to "mixtures containing TMBs". Likewise, clearly indicate that the animal short-	S

				term spatial memory studies were by inhalation exposure (in contrast to the lack of oral exposure studies noted in the first sentence).	
34	1.1.2 and 1.1.4	48, 54	The concentrations used in the study should be listed individually (as in Tables 1-1, 1-2, and 1-4) rather than as a range (as in Tables 1-3 and 1-5); the absence of this information limits the utility and clarity of the summary tables. Such clarity is necessary to review other statements in the document.	Revise Tables 1-3 and 1-5 by listing each nominal concentration, to better describe the study and match the format used elsewhere in this section.	E
35	1.1.3	51	In the second sentence of this section, the document switches from a summary of the lack of human data to discussing animal data without identifiying the species.	At first use, note that the study was conducted with rats. We also suggest that the human and animal data be discussed in separate paragraphs (or separate sections, if the amount of data warrant).	E
36	1.1.4	54-55	On page 55, paragraph one, last line, it is described NOAEL and LOAEL determined from these acute exposure studies are provide in Table 1-5, but in the table only LOAELs are described.	Please clarify and correct.	S
37	1.1.4	56	In the first paragraph, line 3, the years (2000, 1997) are provided, but no authors' names are cited.	Please clarify and add authors' names.	E
38	1.1.5	56	Borriston Laboratories (1984) study administered 1,2,4-TMB to Fischer-344 rats by gavage for 4 weeks and examined nephrotoxicity. Although a minor contribution, this study seems to be missing from EPA's	Please add a mention/reference for Borriston Labs (1984)	E

			assessment.		
39	1.2.2	64	It would be helpful if this table included the neurological endpoints; it would also make it more consistent with Table 1-6.	Add neurological endpoints to Table 1-7.	E
40	1.3	66	Only one report (Maltoni et al 1997) is provided as weight of evidence for carcinogenicity. No discussion is provided to support the WOE concerning the mutagenic mode of action.	Suggest adding the negative results in several key mutagenicity assays in Salmonella and the negative gentoxicity data from the in vivo assays for micronucleus formation in mouse bone marrow cell to show a stronger WOE toward lack of mutagenic potential.	S
41	2.1.1	68	EPA has chosen, in this assessment, to conduct the benchmark dose analysis using external dose as the input, rather than an internal dose, as was used in the recent TCE and methanol assessments. The previous approach, of using internal dose as the input, has a greater toxicological relevance, and should be used in all assessments. We note that the weekly average venous blood concentrations do not have a linear relationship with dose/concentration (e.g., POD ADJ = 0.187 mg/L at 174.1 mg/m3 vs. 0.867 at 492 mg/m3, for Korsak et al., 2000), so the order of the two steps (BMD analysis and internal POD estimation) could have an impact on the candidate RfC.	EPA should redo the analysis with PBPK modeling first, BMD analysis second, for all endpoints. At a minimum, EPA should redo the analysis for the key endpoints to identify the impact of this change from the approach used in the TCE and methanol assessments. EPA should update the draft BMD guidance to reflect this consideration.	S
42	2.1.1	69	The rationale for choosing the weekly average venous blood concentration, rather than the seemingly more toxicologically relevant metric of	We suggest that EPA change their choice of internal dose metric, or provide a scientific rationale (preferably with references) for the	S

			weekly average concentration in the richly perfused tissues should be explained. The impact of this choice should be determined via PBPK modeling.	currently selected dose metric.	
43	2.1.2, 2.1.6, 2.2.2	69, 78, 85	None of the HECs/HEDs can be verified because the model code has not been made available to the reviewers. (This reviewer could not find it on the HERO website, as reported in Appendix A.)	All necessary supporting information, including model code, should be available to all reviewers at all stages of the review, including interagency and external reviews. Without the availability of such data, it is not possible to provide an adequate scientific review.	S/M
44	2.1.2	71	EPA has conducted the interspecies extrapolation prior to the application of uncertainty factors, despite demonstrated nonlinear relationships between external and internal concentration in rats (page 68) and humans (page 85).	EPA should apply the uncertainty factors to the internal point of departure (derived from BMD modeling), then use the human PBPK model to derive the RfC. At a minimum, EPA should apply this alternative approach and provide the results so that the impact of their choice can be clearly identified (and discussed along with other uncertainties). Moreover, as this appears to be a common practice, EPA should provide a reference and a rationale for the procedure, for transparency and clarity, so that reviewers can determine if EPA is being consistent in its procedures for evaluating chemicals. When such inconsistencies are observed in the absence of a written document for reference, it is not possible for reviewers to provide chemical-specific comments on such cross-chemical inconsistencies.	S/M
45	2.1.2	71	EPA has underutilized the PBPK model with	EPA should conduct a sensitivity analysis of the	S

			respect to the insights that can be gained regarding uncertainty factors. A sensitivity analysis of a relevant human internal dose metric (e.g., blood or RPT AUC) at the HED/HEC would help identify parameters that have an impact on EPA's selection among the dose metrics that could, especially in this case where significant nonlinearities are obvious, significantly affect the estimated RfC. It is possible that human variability in, for example, "expression of enzymes involved in 1,2,4-TMB metabolism" may have minimal impact on dosimetry in other tissues, and support the use of a lower value for UFH.	human PBPK model to aid in the identification of a scientifically robust value for UFH, rather than using the default value. As external review peer review panels have repeatedly requested such sensitivity analyses of PBPK models, DoD also recommends that such an analysis should be part of the standard practice for EPA's use of PBPK models, and be performed prior to the external peer review. As the results of such an analysis are expected to significantly influence the reviewers' opinions of either the choice of dose metric or appropriate use (or magnitude of) uncertainty factors, and EPA prefers not to provide an opportunity for public or peer review comment after the external peer review, DoD suggests that all such analyses should be provided to the external peer reviewers and public stakeholders.	
46	2.1.2	71	When assigning the UFD the strengths and limitations of the database need to be more clearly discussed. EPA should integrate the available information and discuss the overall strengths and weakness of the database.	DoD recommends EPA use an integrative approach when discussing the strengths or weaknesses of the total database. The existing data may provide insight as to whether additional information may be needed. EPA might consider (1) developing a standard table that shows presence and absence of data based on type of study, route, duration, species, sex, life stage and general endpoints examined and (2) using a qualitative and integrated look at the total database to inform decisions on the underlying uncertainty. We encourage EPA to move away from making generic statements	S

				about the available database and make an informed decision about critical data gaps.	
47	2.1.2	71	As noted above (comment on Preamble section 7.6, page 15), UFA = 3 is understood to encompass both toxicodynamics and residual toxicokinetic uncertainty after dosimetric/allometric adjustment, per U.S. EPA (2011b).	EPA should revise the text to more accurately reflect the UFA rationale described in U.S. EPA (2011b).	S
48	2.1.2	71 and 73	EPA does not appear to have considered the possibility of using any value other than 10 for UFS. Considering the modest differences in magnitude of effect between acute, short-term (4 week) and subchronic studies, UFS ~4 (Hasegawa et al., 2010) or lower should be considered. Reference: Hasegawa et al. (2010). A proposal of new uncertainty factor application to derive tolerable daily intake. Regul. Toxicol. Pharmacol. 58:237-42.	EPA should reduce UFS from 10 to a lower value or explain why they have not done so.	S
49	2.1.2 and 2.1.6	72, 80	EPA says there is no information on the transfer of 1,2,4-TMB or 1,3,5-TMB across the placenta. As noted by Saillenfait et al. (2005), fetal blood TMB levels were 55-98% of maternal TMB levels in a rat study (Ungvary et al., 1983) and TMB was identified in cord blood of term infants (Dowty and Laseter, 1976). We have some concern regarding the review of the literature.	EPA needs to revise their statements regarding the lack of data on TMBs' ability to cross the placenta and reference these studies.	S/M
50	2.1.5	74	EPA does not discuss uncertainties due to the	EPA should conduct the analyses needed to	S/M

			order in which they have conducted various steps in the RfC process (rat internal dosimetry calculations, BMD analysis, uncertainty factor application, interspecies and route-to-route extrapolation), or note the change from the process previously used for TCE and methanol.	provide quantitative information on the impact of these choices, document them in the Toxicological Review, and discuss them as appropriate. EPA should also provide references, if available, so that reviewers can determine whether these decisions have been suggested by others or are policies that have been generated within the IRIS program and have not been externally peer reviewed.	
51	2.1.5	74	This section states that no information is available to identify a biologically significant decrease in maternal weight gain, and thus uses a BMR based on a change equivalent to 1 SD of the control mean.	EPA should apply the well-established criterion that a 10% decrease in (absolute) adult body weight is an adverse effect, rather than conduct the analysis based on weight gain.	S
52	2.1.5	74	There is no reference to support the assertion that a 5% decrease in fetal body weight is a biologically significant response because developing organisms "may" be more sensitive to such changes.	EPA should provide references for this assertion, or redo their analysis using the 10% decrease in body weight applied to adult animals.	S/M
53	2.1.5	75	EPA notes that no PBPK model exists for 1,3,5-TMB.	EPA should explain why they did not develop a PBPK model for 1,3,5-TMB, given that the existence of the 1,2,4-TMB model and similar kinetic data sets should have given EPA a substantial head start in developing such a model. For other chemicals, EPA has decided to either significantly modify or develop *de novo* PBPK models. EPA should provide the rationale for not taking such action in this case, and also provide decision criteria for when it will modify	S

				existing models. Without such criteria, it is not possible for reviewers and stakeholders to determine if EPA is being consistent in its evaluation and allocation of resources.	
54	2.1.5	76	EPA did not carry forward the decreased pain sensitivity NOAEL identified by Wiaderna et al. (2002) for POD, HEC, and candidate RfC calculation.	EPA should carry forward the decreased pain sensitivity finding for 1,3,5-TMB exposed animals reported by Wiaderna et al. (2002) as additional comparative information for its proposed 1,3,5-TMB RfC.	S
55	3	92	DoD suggests that EPA provide documents (preferably available on web sites) rather than the text of web site (EPA, 2011a, "IRIS Process Retrieved August 24, 2011") Text of web sites change as do URLs. A document with a title and a reference number can still be retrieved.	Please make the cited text a document that is unlikely to change over time.	E
56	Appendix A	A-7 and elsewhere	There are numerous typographical errors throughout Section A.1 with respect to referencing tables and figures, mostly within the text, but including citations in Table A.1-7. For example, Page 7, Figure C-1 should be Figure A-1. Table A.2-1 should be Table A.1-1. Moreover, all of the appendices are individually listed in the Table of Contents as starting on page 94 when they do not. It is difficult to perform a review when references are incorrect. We believe that the software used to create these documents allows insertion of	EPA should thoroughly check the citation of tables and figures throughout this section.	E

			codes so that the Table of Contents (and also references) is automatically constructed and can be quickly updated.		
57	Appendix A	A-9	No units are provided for alveolar ventilation in Table A.1-2, limiting the utility of this summary table.	Add units (liters/min?) for alveolar ventilation in Table A.1-2.	E
58	Appendix A	A-9 to A-10	Text is duplicated from page A-7.	EPA should delete one copy of this text, and if desired, cite the section where it is retained.	E
59	Appendix A	A-13	Text needs to be reworded.	Change "A lung compartment is used to describe for gas exchange" to "A lung compartment is used to describe gas exchange".	E
60	Appendix A	A-16	EPA states that revised model code and modeling results are available on EPA's HERO database. We did not find any such information there.	As noted above (comment on p. 69), all the necessary supporting information, including model code, should be made available to all reviewers at all stages of the review, including interagency and external reviews.	S/M
61	AppendixA	A-24	"Minimize" is used where "maximize" was meant (see page A-25 for increase in LLF).	Change "minimize" to "maximize".	S
62	Appendix A	A-26	All of the figure and table references within Table A.1-7 are incorrect. Unlike other locations, the errors will not be corrected by changing all "A.2" references to "A.1". For example, the venous blood data of Swiercz et al. (2003), the key toxicokinetic data set, were depicted in Figure A.1-9, not Figure A.2-8.	Correct the figure and table references.	E/M
63	Appendix A	A-32	There appears to be a typographical error for the model predicted venous blood concentration at	Verify that the model value should be 4.21 mg/L, rather than 74.21 mg/L, and change the table	E

			75 ppm.	entry. As with other comments, we are concerned about errors in reporting data from the literature. Neither DoD nor most of the public stakeholders have the resources to perform a quality control check of all the data provided in the draft document. While we have provided examples of errors we have observed, we are concerned that there are likely others that were not found. We encourage EPA to institute QA/QC procedures that ensure that all data that are reported in the document are accurate prior to external review of its document.	
64	Appendix A	A-37	While sensitivity analysis of PBPK models for test species are very useful to verify parameter identifiability, as documented here, further sensitivity analyses of the human model would also be very useful to inform the selection of UFH and to identify potentially pharmacokinetically sensitive subpopulations.	EPA should conduct a sensitivity analysis of human steady state blood or tissue concentrations of 1,2,4-TMB at the HEC and HED or RfC and RfD.	S
65	Appendix B	B-6	EPA asserts that "a 5% decrease in body weight was determined as biologically significant for prenatal rats", but provides no references for this assertion.	As previously noted (comment on page 74), EPA should provide references for this assertion or redo their analysis using the 10% decrease in body weight applied to adult animals. DoD suggests that EPA should follow standard toxicological practices, or provide a rationale as to why such practices are not valid for this chemical.	S/M
66	Appendix B	B-8 and following	While EPA notes that scaled residuals may be	EPA should add information on relevant scaled	E

		tables	used to assess model fit (page B-7), they do not provide that information in their tables. Thus, external reviewers are not able to independently determine if such criteria have been appropriately considered by EPA in its selection of the model from which the POD is determined.	residuals both for clarity and to allow independent review of its actions.	
67	Appendix B	B-8 and following figures	BMDS figure outputs do not provide units. Units should be provided in the legends.	Legends of all BMDS figures should note the units for the dose/concentration.	E
68	Appendix B	B-12	Table B-7 footnote “a” contains an error: the p-value cannot = 0.0.02286.	EPA should correct footnote a of Table B-7.	E
69	General		We have noted several typographical errors in our review, but also want to note that there are incomplete sentences, missing verbs and other minor editorial issues that require correction	Suggest having a tech editor review the document in addition to a QC review.	E

Department of Defense Comments on Trimethylbenzenes IASC draft charge

Comments submitted by: Chemical Material Risk Management Program	Organization: Department of Defense	Date Submitted: 2/9/2012

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	(A) 1.	1	DoD would like to add "accurate" to the evaluation of the overall assessment of the document on which the reviewers are asked to opine.	Please add "accurate" to the list of "[accurate], logical, clear and concise" in the first sentence. Please also add "accurately" to "clearly [and accurately] presented and synthesized"	S/M
2	General		DoD greatly appreciates the introductory material that EPA has supplied in this new format for IRIS document. We provided many comments on this section, including some instances where our reading of EPA's guidelines and guidance appears to differ from that presented in the text. DoD assumes that this text will be in each forthcoming IRIS document. While we commend EPA for its efforts, we suggest that EPA have this section separately reviewed by an external review panel whose members have	EPA should clearly identify the introductory material as new for the IRIS process. EPA should note that issues have been raised by interagency reviewers and ask the panel members if they have carefully reviewed that material, if they have provided comments on that material, and if they feel they have expertise and the available resources (e.g. time) to review it. Alternatively, if EPA agrees with DoD, the charge to the peer reviewers could clearly state that the introductory material is not part of their assigned review, that it will be released for	S/M

			expertise in EPA's guidelines and guidance and/or regulatory risk assessment procedures. Ideally, this should be completed before the text, and any chemical-specific decisions made based on the text on which issues have been raised, is released for public comment and external peer review. As DoD understands that the external review panel for trimethylbenzes will be select for expertise for a chemical-specific review, DoD suggest that, if EPA disagrees with the idea of reviewing the introductory material separately, the experts of the panel be asked their opinions of this issue.	public comment and externally peer reviewed before it is included in any final IRIS document, and that it should only be of consideration in their review if this document contains decisions that depend on the statements on which issues have been raised.	