Department of Defense Comments on
EPA's Reanalysis of Key Issues Related to
Dioxin Toxicity and Response to NAS Comments, Volume 1

Comments submitted by: Robert Boyd	Organization: Department of Defense	Date Submitted: 11/30/2011

*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		The rationale for separating the assessment into two volumes was not described to these reviewers and could be problematic for DoD cleanup projects (i.e., potential for confused consideration to use (issue) the non cancer reference concentration in advance of the oral slope factor for assessing cancer risks). This comment is driven by the realistic scenario where requirements to assess sites using first a new dioxin non cancer values, then followed perhaps a year or more later by a new cancer toxicity value would cause sites to be addressed twice. Sites closed out using the reference concentration may have to be reopened once the slope factor is released; this would cause undue utilization of resources and add further confusion with our public stakeholders.	EPA should consider issuance of the Dioxin Reanalysis in one volume; thus issuing non cancer and cancer toxicity values at the same time.	S/M
2	4	Page 4-18, line 8	This statement is not consistent with the citation guidance: "For continuous endpoints, the preference was for models with an asymptote term (plateau for high-dose-response) because continuous measures do not continue to rise (or fall) with dose forever; this phenomenon is particularly evident for TCDD." Even dichotomous endpoints, e.g., cancer, developmental abnormalities, and death, plateau at sufficiently high doses.	EPA should either provide a scientifically accurate reason for its selection of this model or delete the citation and the following sentence.	S/M

3	4.2.4.2. Benchmark Dose Modeling of the Animal Bioassay Data	last paragraph	The procedures given in this paragraph contradict the BMD TG cited as the reference for the procedure. While the BMD Technical Guidance states that the BMRs of 10% or 1 SD should be reported for the purposes of comparison, that document is clear that the BMR should be selected based on the available data. Thus, if the data were such that “many of the TCDD data sets failed to show a response near the BMR”, the BMR should be changed, rather than the more scientifically inaccurate procedures that were indicated in the previous paragraph.	DoD recommends that EPA follow its guidance rather than asserting that the same BMRs must be used for all data sets. If this is a new IRIS policy, DoD would like to have a reference citation of this policy, as it disagrees with the EPA policy in general. Especially as, for the same uncertainty factors, selection of a higher BMR would lead to a higher RfD. This change in EPA’s standard procedures raises the issue of EPA’s statements about the concordance of the candidate RfDs.	S/M
4	4.3.6.1	4-32 - 4-33	In response to the SAB comment to incorporate studies with dioxin-like chemicals into a qualitative discussion of the weight of evidence for non cancer endpoints EPA added a discussion of Goodman et al. (2010) on DLC exposure and thyroid hormone levels in children. There are many that would read the Goodman weight of evidence report and conclude that utilization of thyroid hormone levels as an endpoint for development of an RfD that would be below background levels does not make good scientific sense. The document does not make full use of the Goodman's analysis of over 20 studies. It is not clear why the analysis of T4 levels was not discussed at all when the Executive Summary states that "An increased TSH level is an indicator of a potential decrease in circulating T4 levels, which could eventually lead to neurological deficiencies." This subsection the document discusses adult animal TSH data, the relevance of this is not clear given that the Michigan study was dismissed because it was limited to adult humans and did not examine the sensitive subpopulation. Given that the NAS reviewers recommended that "EPA should incorporate and integrate the relevant	The document gives the impression that EPA is picking and choosing how to incorporate DLCs in its weight of evidence analysis. We suggest that EPA consider the weight of evidence of over 20 studies presented in Goodman et al. in light of the fact that only one study showed an association between TCDD and TSH levels in neonates. We also suggest further consideration be given to the Michigan study.	S/M

			data from both human and animal studies, as appropriate, according to the levels-of-evidence hierarchy devised." It seems that adult human data would be as relevant for discussion here as the adult animal data.		
5	Exec. Sum, Appendix A, 4.4, 4.5, Tables C-1 and C-2	C-149-152, 4-41-4-51	Due to the ubiquitous nature of dioxins (more than 90% of human exposure is through food, mainly meat and dairy products, fish and shellfish), all people have background exposure, which according to WHO, 2010, "*is not expected to affect human health. However, WHO 2010 states that due to the highly toxic potential of this class of compound, efforts need to be undertaken to reduce current background exposure*." WHO recommends that this should be accomplished by reduction in incinerator emissions. As was mentioned by one of the recent dioxin SAB peer review panelists, only modest mention was made of acutal measured dioxin levels in Americans (e.g., CDC biomonitoring data, autopsy reports, etc.) for dioxins, DLCs, and PCBs. Thus, as a panelist stated, it is crucial for EPA to address whether TCDD is a human carcinogen at relevant low environmental levels based on the current weight of evidence. A regulatory agency needs to consider the impact of their non-cancer and cancer health risk analyses as it is such an important consideration so health risk assessors and risk communicators to be able to correctly respond to risk managers and the concerned public who will question whether they or their offspring will get cancer, or not be able to conceive children from ingesting a little more than current U.S "background" levels of dioxins and DLCs in common foods and drinks (e.g., a cheeseburger). EPA should direct the public to the health agencies that can help them decide, for example, the potential adverse impacts (if deemed truly "adverse" by the public health experts) from lactational exposures (current U.S. human lactation exposure from (biomonitoring data) to dioxin and DLCs level ranges compared to EPA's draft toxicity values for the neonate and young child (and women of childbearing age) (sees also Mocarelli et al., 2011, "*Perinatal exposure to low doses of dioxin*	It is essential to provide a much clearer characterization of uncertainties to inform readers, the public and policy-makers what the scientific evidence does and does not establish about the carcinogenicity [and non-carcinogenicity] of TCDD. As an SAB reviewed suggested, EPA should better develop the relationship between dioxin exposure and diet, particularly for fetal and early childhood sensitive subpopulations. Genetic differences should also be discussed in greater detail, especially in light of comparisons to populations with acute exposures and those with differing diets, and ethnicities.	S/M

			can permanently impair human semen quality." These authors conclude based on a study of a small number of Seveso participants: "*In utero and lactational exposure of children to relatively low dioxin doses can permanently reduce sperm quality*." The proper federal agency needs to better understand the ramifications in light of CDC's latest biomonitoring data, mainly related to food and drink consumption, particularly for those considered subsistence "fisher" populations. As an SAB panelist stated, *The* public comments I heard in June suggest that this basic uncertainty about whether TCDD is a human carcinogen (or has adverse effects in humans) at relevant exposure levels, is not being effectively communicated to the public. Also, see Paolo Boffetta et al., 2011, *TCDD and cancer: A critical review of epidemiologic studies*." These authors state, "*In conclusion, recent epidemiological evidence falls far short of conclusively demonstrating a causal link between TCDD exposure and cancer risk in humans*."		
6	Appendix A	Global	EPA has retained a Hill coefficient, used for both cancer and non-cancer evaluations, of less than one. <u>EPA has not responded to the biological issue raised by use of a value less than one, i.e., (page A-13, line 17) "use of a Hill coefficient value well below unity would lead to a nonlinear model behavior that is biologically implausible (hypersensitivity to induction at doses near zero)."</u> DoD agrees with the SAB that biologically implausible predictions should not be used when modeling dose-response functions. EPA's sensitivity analysis agrees with the SAB analysis that the Hill coefficient has the greatest effect on the quantitative results. EPA's justification for retaining its Hill coefficient is that "any change in the Hill parameter would also necessitate changes in optimized variables in order to maintain an adequate fit with the data." <u>DoD suggests that if "adequate fit" of the model requires assumptions of "biologically implausible predictions" perhaps the model needs revision.</u>	EPA should respond to all of the aspects of the SAB's comments, specifically why model fit supersedes biological plausibility. EPA should explain how it interprets the Hill coefficient in the Walker paper and the Emond model, as it is not obvious. If EPA believes that the Hill coefficient should be allowed to vary to improve model fit in conjunction with other parameters, it should apply this criterion consistently across all chemicals or provide a scientifically rational explanation as to why it usually sets the value to 1 but will not do so in this instance.	S/M

			EPA's comment in their response that "the Hill coefficient values represent different processes and are not strictly comparable." is cryptic at best. While there may be various interpretations of the Hill coefficient, EPA does not explain what it views to be this difference either in this response or in the main text of the document. Therefore, the veracity of this statement cannot be judged. In EPA's use of the Hill model to evaluate dose-response for other chemicals, EPA has often set the Hill coefficient to exactly one. If EPA's goal is the "best fit" of the model, does retention of a coefficient less than one signal that EPA will allow the Hill coefficient to vary in its future use of the Hill model?		
7	Appendix A	Global	DoD is concerned that (as expressed in several specific comments below) EPA is unwilling to change any of its analyses, even when it agrees that such changes would result in a scientifically more accurate analysis. EPA's reasoning appears to be that each individual change will have little difference on the result. DoD notes that a change in the Hill coefficient would not only make this analysis more consistent with EPA's previous use of the Hill model but will also make the results (according to its Science Advisory Board) more biologically plausible. Moreover, while some of the individual changes may have relatively minor effects on the outcome, We are concerned that the combined effects may substantially affect the outcome. DoD also is concerned that, since EPA does not carry through its sensitivity analyses to determine the effects on the RfD or cancer potency on the combined changes that the SAB recommended, EPA is not transparent in its response to the SAB's recommendation for a sensitivity analysis. As EPA has performed such analyses in other documents, DoD would recommend it be done here as well.	We suggest that EPA present the RfD (and in Volume 2 the cancer potency) that would be calculated if the Hill coefficient were changed to 1. DoD also recommends that the effects on these values for combined changes recommended by the SAB be provided before EPA implies that the changes would not be significant.	S/M
8	appendix A	A-1	The appendix is not clearly titled. EPA has not provided a summary of	Ideally, EPA should respond to all of the	S

			the SAB's comments, but has only listed those comments that were labeled "Recommendations". Thus, EPA appears to ignore the context of these recommendations and the significant comments in the text of the SAB report.	SAB's comments, not just the recommendations. Otherwise, EPA should clarify the title and text of the appendix.	
9	Appendix A	A-3, line 10	Unfortunately, Figure 4-2 does not respond to the SAB's comment. Under recommendations (SAB 2011, page 13, line 21) the SAB recommended "more discussion and clarity on the exclusion of null epidemiologic studies (for instance the non-cancer thyroid outcome). Figure 4-2 merely illustrates the text that the SAB reviewed, i.e., that EPA eliminated all studies that did not show toxicity. EPA did not further justify this step as requested by the SAB. DoD is particularly concerned that the absence of finding any effect, i.e., the definition of a null study, was by itself sufficient to eliminate a study from further consideration. For example, in Table C-3 Warner et al. (2004) fulfills all of the other criteria, but was apparently eliminated from further consideration by the lack of finding an effect. See also footnote "a" of Table C-3 that states "EPA cannot assess the biological significance of this finding and cannot establish a LOAEL for this effect." This footnote explicitly states that EPA, contrary to the recommendation of its SAB, will continue to ignore null epidemiological studies in its evaluation of the potential for a chemical to cause an effect.	DoD agrees with EPA's SAB that null studies, especially null epidemiological studies, are critical to evaluating the weight of the evidence for toxicity for each endpoint. By eliminating the null studies, EPA may miss a false positive finding when one or more quality null findings could have been used to counter the false positive. EPA should respond to this strong recommendation of the SAB, in particular with regard to the thyroid effects.	S/M
10	Appendix A	A-3, line 12	In addition to the difference across Seveso studies and exposure primarily to TCDD, DoD does not understand how (in Table C-3) the "effective exposure" could be estimated in the one Eskenazi et al. study (2002b) that it chose to use and could NOT be estimated in the three other Eskenazi et al. studies (2002a, 2003, 2005, 2007). All of these studies were labeled by EPA as the Women's Health Study, so DoD assumes they were the same population. Comparing reasons provided	EPA should resolve these inconsistencies, especially with the same study population. Moreover, especially with a document that EPA views as essentially the final version of a major analysis of a controversial chemical, reviewers should not have to parse tables in a more than 200-page	S/M

			in Tables C-31 and C-32, the only difference is that for the study EPA used, effects apparently differed between "women that were premenarcheal at the time of the accident (12 years)" and all other women. Given that contemporary serum levels were obtained in the rejected study and no serum levels were mentioned in EPA's analysis of the accepted study, DoD's conclusion is that the expected exposure would be MORE accurate in the rejected study.	appendix to find contradictions that should have been resolved by EPA scientists. There may be other reasons to reject Eskenazi et al. (2002a), but the reasons outlined in Appendix C for inability to estimate exposure are not logically consistent.	
11	Appendix A	A-3, line 13	DoD does not understand how people exposed to TCDD and other combustion products can have different exposures depending on who is studying the population. In Table C-2, EPA is inconsistent on whether the exposures from the Seveso Cohort were primarily to TCDD. For 3 of the studies, EPA concludes that exposure was NOT primarily to TCDD, but for 2 of the studies, including one selected as a critical study for developing a toxicity value, EPA concludes that the exposure was primarily to TCDD. Yet the populations studied all had the same exposure from the same accident. Similar inconsistencies are found for the Seveso cohort in Table C-3.	EPA should either explain how they determined that, for the Seveso cohort, some epidemiologists studied people who were primarily exposed to TCDD and other epidemiologists studied the same population that was not primarily exposed to TCDD.	S/M
12	appendix A	A-3 line 16	There are some fundamental editorial issues that need to be addressed prior to document finalization such as missing references and documents cited without associated references. Editors should check the reference list and ensure that each reference in the list was used.	Consider editing the document throughout.	E/M
13	appendix a	A-3, line 19	EPA's online glossary, at least at the time of this review, does not contain some critical definitions. Moreover, EPA's added text introduces some novel terms (specified in other comments) that also are not in the IRIS glossary.	EPA's response to this SAB comment is not sufficient, as EPA uses terms that are critical to the understanding of the document that are not in the glossary. Since this review, EPA has added new terms to the text that adds to the lack of clarity that was part of this comment.	E/M

14	Appendix A	A-4, line 1	The added text is neither accurate nor complete. Added Text Box 2-1, for example, cites EPA's 1986 cancer guidelines, as well as EPA's 2005 cancer guidelines, though the former were superseded by and replaced by the latter. Reference to the EPA Framework for Assessing Health Risks of Environmental Exposures to Children is lacking, this guidance was cited several times by the SAB review panel. EPA's exposure guidelines are cited, but no reference is provided in Chapter 5. EPA's developmental guidelines are cited twice, correctly only the second time.	EPA should correct the errors in Text Box 2-1 and elsewhere.	S/M
15	appendix A	A-4, line 1	The numbered criteria in the section referenced in this response, i.e., "2.3.1. Study Inclusion Criteria for TCDD Epidemiologic Studies **"**do not contain a citation. Therefore, we assume they were developed for this document. Indeed, some of these "criteria" contain concepts that appear inconsistent with standard toxicological and epidemiological practice. For example, #3 on page 2-8 that specifically discusses null studies does not mentions the ability of a null study to establish an upper limit on the potency of a chemical (that is discussed in other IRIS documents) nor does it mention the utility of null studies to address the issue of false positive results. Moreover, EPA's use of the term “free-standing NOAEL” is neither defined in the text nor in the online IRIS glossary.	EPA should address the well-known utility of null epidemiologic studies. In its new text, EPA should refrain from introducing terms that are neither defined in the text, nor in the IRIS glossary, nor in common usage in other EPA documents.	S
16	Appendix A	A-4, line 1	In the section referenced in this response, i.e., "2.3.1. Study Inclusion Criteria for TCDD Epidemiologic Studies**",** the criteria that are in the second section are labeled "three specific study inclusion criteria". Number 3 in this section (page 2-9) contains requirements that would not be required for all epidemiological studies. Moreover, <u>the requirement of a "biologically-relevant critical exposure window of susceptibility" suggests that the criteria are based on the assumption that reproductive effects would be the most sensitive -- that provides an inherent, prior bias into the selection of the studies</u>. Many, if not most,	EPA should refrain from using criteria that impose conditions that are not appropriate for all toxicological endpoints, as this introduces an inherent bias. EPA's use of novel terms that are neither defined in the text nor in the IRIS glossary impedes transparency and clarity.	S

			toxicological endpoints do not have a critical window of exposure, e.g., formation of carboxyhemoglobin, enzyme induction, mutations, liver enzyme induction, hyperplasia. Moreover, neither "critical exposure window" nor "critical window" appears in the IRIS glossary. While the SAB stated that the draft document contained "a considerable amount of jargon", this version has added more unconventional jargon.		
17	appendix A	A-4, line 1	The selection criteria that have been added in "2.3.1. Study Inclusion Criteria for TCDD Epidemiologic Studies" are new to the IRIS process and have not been those under which epidemiological studies have been evaluated previously. <u>These criteria were not available to the external peer reviewers, nor the stakeholders who participated in the public comment period. To the best of our knowledge, these criteria are not in any written documents available from EPA; thus, they have neither been peer reviewed nor has the public been given the opportunity to comment on them -- as the public will not be allowed to comment on this draft.</u> DoD provides comments on some of the specific issues these criteria raise, though we have not had time to review them completely.	Inclusion/exclusion criteria are unbiased only if they are established prior to review of the studies. As these sections were added after the review was completed, we cannot be certain when they were developed. If they were developed early in the process, EPA had time to obtain the appropriate review process -- which DoD would encourage. Ad hoc, chemical-specific criteria should not be used. DoD strongly recommends that EPA develop a set of criteria for the use of epidemiologic studies and have them undergo the standard external review and public comment to ensure their lack of bias and transparency.	S/M
18	Appendix A, Table C-40, 4.3.6.1; 4.4, 4.5. Figure 4-7	A-5 Lines 15, 16; C-211	The SAB panel report recommended that EPA provide a discussion on the strengths and weaknesses of the studies used to derive an RfD and include whether these weaknesses affect the RfD determination. As a panel member stated, there are many causes of elevated neonatal thyroid stimulating hormone (TSH), including iodide uptake inhibition (e.g., from insufficient iodine in the diet, from ingestion and/or environmental exposure to thiocyanate, nitrate), from exposure to other common "ubiquitous and persistent" chemicals besides TCDD, from errors in the screening procedures, food intake, prematurity, severe	A more careful and critical review of the Baccarelli et al., 2008 increase TSH finding in regard to the robustness of this study as a "co-critical" study is highly recommended, especially in light of the weight of evidence supported by several larger studies of maternal-infant pairs that reported no statistically significant increase in TSH	S/M

			illness, maternal thyroid disease, gestational age, maternal iodine levels. None of these were fully discussed or noted in the Reanalysis. Other markers of thyroid function, such as total thyroxine (T4), free T4, and total triiodothroxine (T3) were not discussed as was not the body's own protective mechanism to produce more T4 (feedback loop) and whether increased TSH is considered upstream of a clinically significant adverse effect, such as a decrease in neonatal T4. We understand that using an increase in TSH (Baccarelli et al., 2008) is a conservative, health protective approach but agree with the SAB panel thyroid experts that the document would be improved with a discussion of reversibility issues, especially in regard to biochemical changes in TSH and no data on total and free T4/total and free T3 changes. However, establishing a causal connection with the non-cancer "critical effects" noted in the selected studies is very difficult.	(Goodman et al., 2010) Include a discussion of reversibility issues, continuum of change in regard to thyroid homeostasis, other potential confounders, and conflicts in the scientific literature concerning studies reporting increases in TSH with increases, not anticipated decreases in T4. (e.g., Goodman JE et al., 2010, etc.).	
19	appendix A	A-6	This page states that EPA deleted a number of the qualifiers in the criteria used for study selection. Yet the results with regard to the designation of the critical studies are identical. Perhaps this is the reason DoD finds inconsistencies in the tables that are cited as the response to these issues. DoD cannot locate where these inconsistencies are resolved.	EPA needs to resolve the inconsistencies that its changed criteria and more transparent presentation of the selection of critical studies have demonstrated. <u>Until these inconsistencies are resolved, the selection of the critical studies cannot be justified.</u>	S/M
20	Appendix A	A-7, 2-8	An SAB reviewer questioned how "null" studies related to TSH were dealt with in EPA's consideration of association of dioxin and DLCs exposure and potential changes in TSH, the reviewer recommended more discussion and clarity. According to the revised draft, EPA states that a "*free standing NOAEL from a study in which* no adverse effects have been *observed is not usually chosen for RfD derivation when other available studies demonstrate LOAELs*." The positive studies are considered stronger candidates for derivation of the RfD. Page 2-8 states that "*The study demonstrated an association between TCDD*	Provide stronger justification based on study merit and design and a more detailed discussion of null studies and relevance to potential "adverse" thyroid effects from current body burden levels of dioxin and DLCs in the U.S. population. EPA's justification for not using null epidemiology studies appears biased and does not adequately respond to the significant SAB	S/M

			and an adverse health endpoint" [increased TSH]. "*This consideration in effect rules out the use of a null study"* (i.e., a study reporting no association between TCDD and the health endpoint of interest in the quantitative dose-response assessment used to derive the RfD). Thus, it appears that EPA dismisses many robust studies, as Goodman et al., 2010 states, of the 23 relevant epidemiological studies of dioxins and dioxin-like compounds (DLCs), chlorinated dibenzofurans and mon- and non-ortho polychlorinated biphenyls (PCBs) that measured exposures to various dioxins and DLCs and markers of thyroid function in cord blood or circulation, the majority of observed associations were not statistically significant. Moreover, there were no clear and consistent effects across studies for any of the hormone levels examined (TSH, free and bound T4 and T3, etc.) and in actuality, other studies showed either no change or changes in the opposite direction for the same thyroid marker. There were no clear correlation between background exposure to dioxins and DLCs during development (birth - 12 years) and thyroid function.	consensus to consider them in determining the weight of evidence (that is, NOAEL, etc.).	
21	Appendix A	A-10, line 6	We were surprised to see all of the studies suggested by a member of the public dismissed by EPA, even for purposes of hazard identification. While EPA is entitled to such a position, DoD believes that it would be useful for EPA to provide further details regarding why they are not useful. It is not clear why EPA did not consider the "University of Michigan Dioxin Exposure Study: Predictors of human serum dioxin concentrations in Midland and Saginaw, Michigan." It appears that the study has pertinent "in vivo mammalian dose-response" information that would be useful in quantitative dose-response analysis for derivation of an RfD or oral slope factor for TCDD.	EPA's apparent dismissal of significant reports, provided by the public suggests that they are not considering alternative data and analyses provided as part of its external review process. DoD recommends that EPA explain rejection of the studies in more detail.	S
22	Appendix A	A-10, line 18	While EPA states that it "collected and evaluated studies through October 2009", DoD cannot find any indication that it reviewed the	The choice of references selected by EPA is neither clear nor transparent. While this	S/M

			massive University of Michigan study that relates exposure to serum levels, as indicated by an electronic search of the references provided in Section 5 of this draft. Although in the previous response, EPA asserts that this study provided no useful information, DoD's review suggests that it provides much data that could be used to either support or reject some of EPA's critical analyses. DoD does not understand why EPA chose not to include any of the references suggested by its SAB, even though it cites similar data from the same laboratories. EPA should specifically address why these references were not considered.	version of the report provides more information on studies it chose to review, it provides no information on why it rejected other studies recommended by the SAB panel.	
23	Appendix A	A-10, line 20	While EPA states that it updated its 2003 analysis through October 2009, it also state that it "included evaluations of several studies published in 2010 and 2011." EPA has not provided any information on how or why it selected these studies, and chose to reject others, including those suggested by its SAB and the public that would have been within the October 2009 time period.	DoD suggests that all studies within a given time period have the same criteria for evaluation in this document. <u>The use of only selected studies beyond October 2009 without any criteria for excluding other studies within this time period does not fit the appearance of impartiality that should be a fundamental consideration in this review.</u>	S/M
24	Appendix A	A-10, line 26	The statement that "EPA's benchmark dose modeling software does not allow for modeling of covariates" is not accurate. EPA's software includes a nested analysis that is specifically designed to model the co-variation between offspring in a litter from one mother as contrasted with offspring in different litters.	EPA should correct this statement.	S

25	Appendix A	A-12, line 10	In their response relative to interspecies extrapolation and the Edmond PBPK model EPA states: "This approach assumes that differences in serum and serum lipid fractions between rodents and humans do not result in large differences among the species in the transfer of TCDD from blood to liver." We view this as a critical assumption that was neither available to the external peer reviewers nor for stakeholders for their public comment.	Critical assumptions, such as this that can significantly affect the quantitative outcome, should have been available for the external peer reviewers. Without this information, the reviewers ability to determine procedures used were greatly limited.	S
26	Appendix A	A-12, line 16	The EPA response does not address the SAB comment that a quantitative evaluation of the impact of model selection on dose metric predictions should be provided.	A quantitative evaluation of the impact of model selection should be added to the Reanalysis document.	S
27	Appendix A	A-12, line 31	None of the existing models had a feature that EPA desired. EPA modified ONLY ONE of the existing models to have this feature. Therefore, none of the other models were relevant because they didn't have the *post hoc* "required" feature. Clearly, since the modifications were, according to EPA "minor" it could modify another model to have this feature and demonstrate the difference in the effect of the models. If EPA only modifies the model that has the most conservative results, its results are not unbiased. Moreover, minor modification and use of two PBPK models would provide one quantitative uncertainty measure for both cancer and non cancer that EPA chose not to perform.	If EPA needs to modify existing models, it should do so in an unbiased manner.	S/M
28	appendix A	A-14, line 1	The response contains errors in specifying the sections. The correct sections are "**3.3.4.3.2.5.** *Sensitivity analysis of the PBPK model***" and "3.3.4.3.2.6.** *Further uncertainty analysis of the Hill coefficient and CYP1A2 induction parameters".* The section listed in the response does not exist.	EPA should review the document for these types of errors and make necessary corrections.	E
29	Appendix A	A-14, line 4	EPA's response does not include the findings of the sensitivity analysis,	To be fully responsive to the SAB's major	S/M

			i.e., that when the Hill coefficient was set to 1, as is the usual case for EPA's use of this model, and the dependent parameter, *kelv*, was optimized, "both values fitting the data equally well" (page 3-44, second paragraph above equation 3-22). As, according to the SAB, the Hill coefficient value of 1 is more biologically plausible and as the model fit is equally good, DoD does not understand why EPA has neither used these data nor calculated the RfD that would have been estimated if this change were made.	concerns about the value of the Hill coefficient, EPA should calculate the RfD that would have been estimated if this change were made. A complete sensitivity analysis not only identifies the most sensitive parameter(s) but also calculates the effect of the change in the most sensitive parameter on the ultimate results. Not only would this be more responsive to the SAB comments, but it would also assist in addressing the SAB's concerns about a lack of a quantitative uncertainty analysis, especially as EPA appears to agree with the SAB that this change could affect the results by at least an order of magnitude.	
30	Appendix A	A-14, lines 11 - 40	EPA's response states that it agrees with the SAB that the value should be closer to 200 than 100; indeed, if EPA had rounded its now preferred value of 160 to one significant figure -- as it has done for other parameters in this model -- it would have the value of 200 recommended by the SAB. Even if EPA chose to keep the value of 160, it has clearly performed all of the analyses necessary to change the RfD based on this change, as it states that the resulting change would be less than 10% of the POD. The UFs would be the same, so dividing the POD by the UFs is minimal extra work. Nonetheless, after performing all of the necessary calculations to obtain what EPA agrees is a more accurate RfD, it states that "there is not sufficient justification to change the parameter value in the model at this time." We do not understand why EPA did not implement this suggestion by the SAB panel.	Given that EPA is unlikely to complete another analysis of dioxin within the next 10 years, DoD recommends that EPA change its RfD to reflect the best analysis it currently can perform.	S/M
31	Appendix A	A-14, through	If the mouse model is not an important factor in the estimate of the RfD,	EPA should be consistent in addressing the	S/M

		A-15	DoD fails to understand why these charge questions are discussed as part of Volume 1, when all of the charge questions on the cancer analyses are otherwise postponed. If this model is important to the RfD, then the comment on lines 17-18 is not accurate.	SAB's comments with regard to the cancer analyses, or correct the sentence with regard to the mouse PBPK model. <u>If the model is important for the quantitative analysis for the RfD, DoD suggests that the entire dioxin analysis, including Vol. 1, be held until the model is externally peer reviewed.</u>	
32	Appendix A	A-15, A-23 - A-24	EPA has not sufficiently addressed the following SAB panel comments in regard to Mocarelli et al., 2008: "*The Panel recommends that discussion of the consideration that "statistical precision, power, and study follow-up are sufficient*" be clarified. "*The Panel recommends that the standard deviations or range of changes in Mocarelli et al., 2008 are discussed in the Report because this provides a better understanding of the potential magnitude of effect*." Children eliminate TCDD from their bodies faster than adults and have a shorter TCDD half-life, possibly due to differences in the relative contribution of toxicant clearance pathways (Kerger 2006). The PBPK model EPA used does not accurately reproduce the elimination of TCDD in children as the EPA model omits a key elimination mechanism: excretion of intestinal lumen-rates in children, which are far higher per kg body weight than in adults. EPA does not present an evaluation of its PBPK model against the available Seveso children elimination rate data. Model results are contrary to data on elimination rates in Seveso children (Kerger et al., 2006). EHP 114:1596. For ages <12, average half-life is 1.5 years. Thus, we believe that EPA significantly underestimates the intake rates required to attain point of departure (POD) concentrations in children. Thus, it appears that the RfD based on the Mocarelli et al. 2008 study would be approximately 3 times higher (about 4 pg/kg/day).	EPA should respond appropriately to the SAB panel's findings regarding the PBPK model used.	S/M

33	appendix A	A-15, line 13	EPA's response is insufficient. If this model is not critical to the RfD, then it must be critical to the cancer results, and DoD strongly suggests that EPA delay release of this portion of the Reanalysis or all of Volume I until the model has been peer reviewed and the results incorporated into the analysis. Final publication of this model absent an external peer review will not allow comments and changes in the model after the review has occurred. EPA should be able to conduct this review and revise both parts of the toxicological assessment within the year that Volume 2 is estimated to be released. If the resulting review and changes make little difference, very little changes will be required. If the changes based on the review significantly alter the results, DoD believes a one-year delay is preferable to releasing a final RfD that is based on an unreviewed model. As EPA has had the SAB's report for months prior to release of this draft, DoD is surprised that the peer review was not conducted while other changes were being made in the document so that this issue could have been resolved before this interagency review.	EPA should not publish the final version of the mouse model at this time as it has not been externally peer reviewed unless it is EPA's position that, even if major changes are recommended, EPA will not revise its analyses.	S/M
34	Appendix A	A-15, line 22	Despite EPA's willingness to rerun some aspects of the PBPK modeling, it appears to be unwilling to respond to the SAB's comment that "The urinary excretion data can be improved by taking into account the fact that urine contains metabolites only, which partition differently from the parent compound."	Given that EPA states that the mouse model was not used for the RfD, DoD suggests that EPA revise the mouse model as suggested by the SAB.	S
35	Appendix A	A-17, line 23	EPA found no models that included urinary elimination, and chose to add this to one of the existing models. However, in regard to the lactational component, EPA responded that they "...found no models pertaining to this life stage." Clearly, EPA could have added a lactational component to the model, and either did not think to do so when it revised the model, believes (without saying so) that it would have little effect (despite information on similar compounds such as PCBs), or is not willing to do so at this time for reasons other than using	If EPA has non-science, policy reasons to not accommodate improvements in the model that were suggested by its SAB, it should so state. Implying that it could not make this modification to the model provides neither clarity nor transparency. Given that this reanalysis has been going on since 2003, implementing the changes	S/M

			the best available science.	suggested by the SAB to improve the accuracy of the model would seem reasonable.	
36	Appendix A	A-23, lines 4-32	The response does not address the SAB panel comment which suggests use of the EPA "Framework for Assessing Health Risks of Environmental Exposures to Children" (EPA, 2006) for addressing the issue of the exposure window and calculation of average exposure.	Please add a response in Appendix A to this SAB comment and appropriate text in the Reanalysis.	S
37	Appendix A	A-23, line 17; A-27, line 1	The data EPA presents directly contradicts the assumption made in EPA's analysis, i.e., an acute exposure such as the Seveso accident, will lead to more severe effects than an equivalent lower exposure level. The SAB states that "several papers have indicated the unique aspects of high peak exposure of TCDD as occurred in Seveso and in several of the animal studies". Apparently EPA disagrees, as they averaged the Seveso exposures and lists several studies in its response to the SAB.	DoD believes that EPA should follow the data and the advice of its SAB and base its RfD on the acute dose received by the children.	S/M
38	appendix A	A-27, line 33	As discussed in a previous comment, the Text Box cited is neither accurate nor complete.	EPA should correct Text Box 2-1	S
39	appendix A	A-28, line 25.	EPA's response is incomplete. While it states that it has performed these analyses, it does not state the outcome. For example, according to Figure 4-7, the resulting POD could be 3-fold higher than the estimate based on TCDD alone.	DoD thinks that a 3-fold difference in a POD, and hence in the RfD is significant. Based on the additional analysis recommended by EPA's SAB, DoD strongly suggests that EPA reconsider the scientific accuracy of its RfD prior to release of this document.	S/M
40	Appendix C	Tables C-4 through C-57	The evaluations of the individual studies are not presented in a rational manner beyond the cancer versus non-cancer divide. The studies are arranged neither alphabetically by author nor by date. Indeed, the 5 Eskenazi et al. studies are interspersed with 2 of the 3 Warner et al.	Reader confusion may be eliminated by reordering the study presentation.	E

			studies. Mortality studies are interspersed with less severe outcomes. This lack of logical organization supports the lack of clarity and transparency noted by EPA's SAB as it is very difficult for reviewers to find the details of the evaluation of individual studies.		
41	Appendix C	C-209, C-210, Table C-38	Mocarelli et al., 2008, results were based on only 71 boys ages 1-9, with only a single semen sample per participant. This is contrary to current practices outlined in the "*WHO Laboratory Manual for the Examination and processing of human semen, 5th edition*," 2010, guidelines, which states, "it is impossible to characterize a man's semen quality from evaluation of a single semen sample". Other ubiquitous dietary and environmental chemicals, such as alcohol consumption, ortho-substituted phthalate esters, dieldrin, etc. have been reported to cause reduced sperm count, and other similar reproductive effects as TCDD. (e.g., see **"***Annex XV Restriction Report Proposal for A Restriction Substance: BIS(2-Ethyl Hexyl) Phthalate (DEHP), Benzyl Butyl Phthalate (BBP), Dibutyl Phthalate (DBP), Diisobutyl Phthalate (DIBP)*," (URL: http://echa.europa.eu/doc/restrictions/restriction_report_phthalates.pdf), which states "*Large internationally coordinated studies on semen quality of men from the general population in different European countries including France, Finland, Scotland, Estonia and Denmark found large differences between the countries and especially in Denmark a large proportion of the men had semen quality in the sub-fertile range*..." "*The endocrine disrupting effects that are suspected to be relevant in humans in relation to the four phthalates are congenital malformations of the male reproductive organs, reduced semen quality, reduced male reproductive hormone levels...*"	EPA should discuss their confidence that the contribution of the actual DLCs and PCB exposures and other endocrine disrupting chemicals may have more greatly contributed to the critical effects experienced by the Seveso population relating to the number of sperm. It would be helpful for EPA to have an expanded discussion of the clinical significance (or lack thereof) and a more detailed analyses of the strengths and weaknesses of all the Mocarelli et al. 2008 findings and potential confounders that may have impacted male sperm count, such as recent weight loss. genetic variables, cell phone usage, exposures to other environmental/dietary contaminants besides TCDD, etc. and comparisons to U.S. and other countries' National averages, etc. (Additional current references can be provided upon request). As an SAB peer review panelist recommended, EPA should compare this point of departure to what would lead to a man being considered infertile today.	S/M
42	Appendix C	C-209, C-	According to EPA, risk estimates based on Mocarelli et al., 2008 are	A more detailed discussion of how these	S/M

		210, Table C-38	not susceptible to important bias or confounding. Aylward and Hayes (2002) estimated a TCDD intake of at least 1.3E-3 ng/kg-day for the U.S., Canada, Germany, and France prior to 1972. These estimates are more than three times higher than EPA estimated using the Edmond PBPK model. It is not clear why EPA does not base TCDD estimates on actual intake measurements instead of being dependent on modeling assumptions.	estimates compare to actual biomonitoring data from other populations needs to be included in the Dioxin Reanalysis for comparison and for purposes of transparency. EPA should also discuss in greater detail the likelihood that the background DLCs exposure from the Edmond model are too low based on other actual and modeled estimates	